

BENZAZEPINE DERIVATIVE, PRODUCTION AND USE THEREOF

Technical Field

5 The present invention relates to a novel benzazepine derivative, production and use thereof.

Background Art

10 Recently, HIV (human immunodeficiency virus) protease inhibitors are developed for method of the treatment of AIDS (acquired immunological deficient syndrome) and use of the protease inhibitors in combination with conventional two HIV reverse transcriptase inhibitors provides with a further progress  
15 of the treatment of AIDS. However, these drugs and their combination use are not sufficient for the eradications of AIDS, and development of new anti-AIDS drugs having different activity and mechanism are sought for.

20 As a receptor from which HIV invades to a target cell, CD4 is so far known, and recently CCR5 as a second receptor of macrophage-tropic HIV and CXCR4 as a second receptor of T cell-tropic HIV, each of which is G protein-coupled chemokine receptor having seven transmembrane domains, are respectively found out. These  
25 chemokine receptors are thought to play an essential role

Ins.  
a<sup>1</sup>

10018321-121201

in establishment and spread of HIV infection. In fact,  
it is reported that a person who is resistant to HIV  
infection in spite of several exposures retains mutation  
of homo deletion of CCR5 gene. Therefore, a CCR5  
5 antagonist is expected to be a new anti-HIV drug.  
However, so far, there has been no report that a CCR5  
antagonist is developed as a therapeutic agent of AIDS.

#### Disclosure of the Invention

10 In order to investigate an anti-AIDS drug having  
CCR5 antagonistic activity, it is necessary to clone CCR5  
gene from human tissue derived cDNA library, to ligate  
said gene with a vector for expression in animal cells,  
to introduce said gene into animal cells and to obtain  
15 cells expressing CCR5. In addition, with using this  
transformant, it is necessary to screen a compound which  
strongly inhibits binding of CC chemokine RANTES, natural  
ligand, to CCR5. However, so far there has been almost  
no report on a low molecule compound which has this CCR5  
20 antagonistic activity and is suitable for oral  
administration. The present invention is to provide a  
novel anilide derivative which is useful for the  
treatment or prevention of infectious diseases of HIV and,  
in particular, AIDS and also which is suitable for oral  
25 administration, production and use thereof.

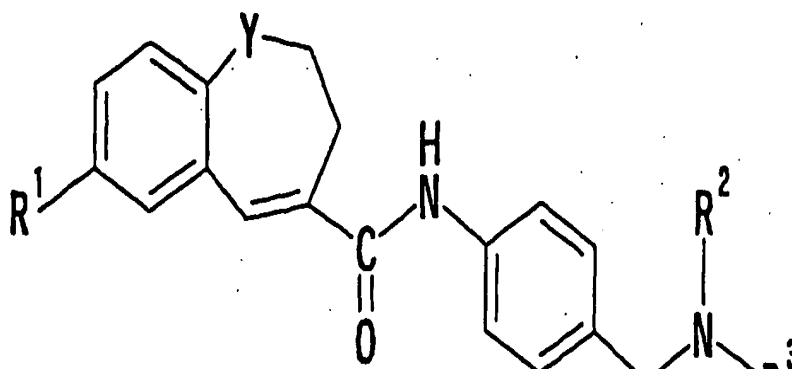
Amen.  
B1

10013331 12001  
T02121

The present inventors diligently made extensive studies on compounds having CCR5 antagonistic activity and, as a result, they found that a benzazepine derivative of the following formula (I) or a salt thereof [hereinafter, referred to as Compound (I) in some cases] possesses CC chemokine receptor (CCR) antagonistic activity, in particular, potent CCR5 antagonistic activity and clinically desirable pharmaceutical effect (e.g. remarkable inhibition of HIV infection to human peripheral mononuclear cells, etc.) and also that Compound (I) has superior absorbability when orally administered. Based on the finding, the present invention was accomplished.

More specifically, the present invention relates to

(1) A compound of the formula (I):



are respectively hetero-atoms, and which may have a further substituent, the group R may bind to the 5- to 6-membered aromatic ring to form a ring, Y is an optionally substituted imino group, R<sup>2</sup> and R<sup>3</sup> are respectively an optionally substituted aliphatic hydrocarbon group or an optionally substituted alicyclic heterocyclic group; or a salt thereof;

(2) A pro-drug of the compound as described in the above (1) or a salt thereof;

(3) The compound as described in the above (1), wherein the 5- to 6-membered aromatic ring is benzene, furan or thiophene;

(4) The compound as described in the above (1), wherein the 5- to 6-membered aromatic ring is benzene;

(5) The compound as described in the above (1), wherein R is an optionally halogenated lower alkyl group;

(6) The compound as described in the above (1), wherein X is  $-(CH_2)_n-$  (n is an integer of 1-4);

(7) The compound as described in the above (1), wherein Z<sup>1</sup> and Z<sup>2</sup> are respectively -O-, -S(O)<sub>m</sub>- (m is an integer of 0-2) or -N(R<sup>4</sup>)- (R<sup>4</sup> is a hydrogen atom or an optionally substituted lower alkyl group);

(8) The compound as described in the above (1), wherein Z<sup>1</sup> is -O- or -S(O)<sub>m</sub>- (m is an integer of 0-2);

(9) The compound as described in the above (1), wherein

10018321.121201



$Z^1$  is -O-;

(10) The compound as described in the above (1), wherein  $Z^2$  is -O- or -N(R<sup>4</sup>)- (R<sup>4</sup> is a hydrogen atom or an optionally substituted lower alkyl group);

5 (11) The compound as described in the above (1), wherein  $Z^2$  is -O-;

(12) The compound as described in the above (1), wherein Y is -N(R<sup>5</sup>)- (R<sup>5</sup> is a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted acyl group);

10

(13) The compound as described in the above (12), wherein (R<sup>5</sup>) is C<sub>1-4</sub> alkyl, formyl or C<sub>2-5</sub> alkanoyl;

(14) The compound as described in the above (12), wherein R<sup>5</sup> is a group represented by the formula  $-(CH_2)_k-R^6$ :

15 wherein k is 0 or 1, and R<sup>6</sup> is an optionally substituted 5- to 6-membered monocyclic aromatic group;

(15) The compound as described in the above (1), wherein R<sup>2</sup> is an optionally substituted straight chain hydrocarbon group;

20 (16) The compound as described in the above (1), wherein R<sup>2</sup> is an optionally substituted lower alkyl group;

(17) The compound as described in the above (1), wherein R<sup>3</sup> is an optionally substituted alicyclic hydrocarbon group or an optionally substituted alicyclic heterocyclic group;

25

10048321.121201

Amen.

B2

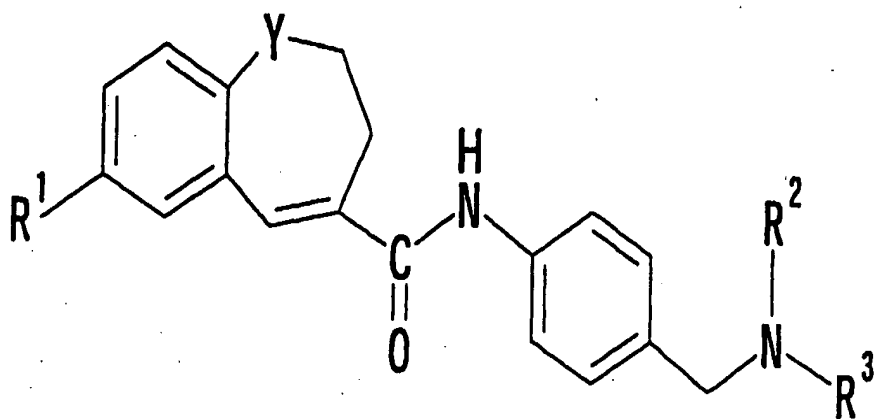
10018321.121201

- (18) The compound as described in the above (17), wherein the alicyclic hydrocarbon group is a lower cycloalkyl group;
- 5 (19) The compound as described in the above (17), wherein the alicyclic hydrocarbon group is cyclohexyl;
- (20) The compound as described in the above (17), wherein the alicyclic heterocyclic group is a saturated alicyclic heterocyclic group;
- 10 (21) The compound as described in the above (17), wherein the alicyclic heterocyclic group is tetrahydropyranyl, tetrahydrothiopyranyl or piperidyl;
- (22) The compound as described in the above (17), wherein the alicyclic heterocyclic group is tetrahydropyranyl;
- 15 (23) The compound selected from the class consisting of 7-(4-ethoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 1-ethyl-7-(4-propoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-
- 20 benzazepine-4-carboxamide,
- 7-(4-butoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 7-(4-ethoxyethoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-
- 25 (tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-

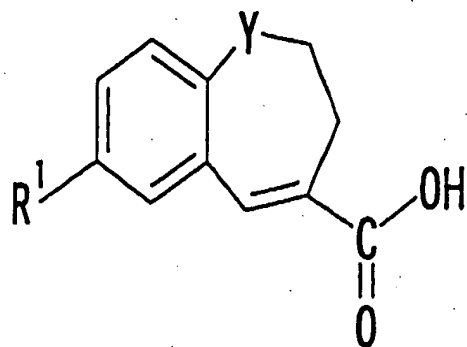
- benzazepine-4-carboxamide,  
 1-formyl-7-(4-propoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 5 7-(4-butoxyethoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-1-propyl-2,3-dihydro-1-benzazepine-4-carboxamide,
- 10 N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-1-propyl-2,3-dihydro-1-benzazepine-4-carboxamide,
- 1-benzyl-7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 15 7-(4-butoxyethoxyphenyl)-1-cyclopropylmethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 20 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-phenyl-2,3-dihydro-1-benzazepine-4-carboxamide,
- 7-(4-butoxyethoxyphenyl)-1-(3,4-methylenedioxy)phenyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-
- 25

- carboxamide,  
7-(4-butoxyethoxyphenyl)-1-(2-methyloxazol-5-yl)-N-[4-  
[[N-methyl-N-(tetrahydropyran-4-yl) amino]methyl]phenyl]-  
2,3-dihydro-1-benzazepine-4-carboxamide,  
5 1-allyl-7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-  
(tetrahydropyran-4-yl) amino]methyl]phenyl]-2,3-dihydro-1-  
benzazepine-4-carboxamide,  
7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-  
(tetrahydropyran-4-yl) amino]methyl]phenyl]-1-(3-  
10 thienyl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide,  
7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-  
(tetrahydropyran-4-yl) amino]methyl]phenyl]-1-(thiazol-2-  
yl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide,  
7-(4-butoxyethoxyphenyl)-1-(1-methylpyrazol-4-yl)methyl-  
15 N-[4-[[N-methyl-N-(tetrahydropyran-4-  
yl) amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-  
carboxamide,  
7-(4-butoxyethoxyphenyl)-1-(3-methylisothiazol-4-  
yl)methyl-N-[4-[[N-methyl-N-(tetrahydropyran-5-  
20 yl) amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-  
carboxamide,  
7-(4-butoxyethoxyphenyl)-1-(1-ethylpyrazol-4-yl)methyl-N-  
[4-[[N-methyl-N-(tetrahydropyran-4-  
yl) amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-  
25 carboxamide,

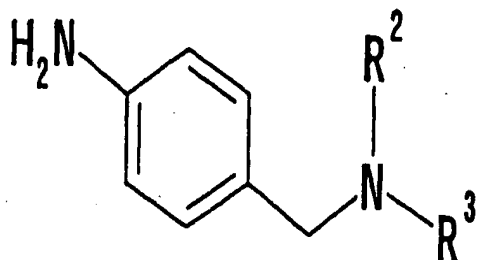
- 7-(4-butoxyethoxyphenyl)-1-isobutyl-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 1-isobutyl-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxamide,
- 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(thiazol-5-yl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide,
- 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(1-methyltetrazol-5-yl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide, and
- 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(2-methyltetrazol-5-yl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide, or salt thereof;
- (24) A pro-drug of the compound as described in the above (23) or a salt thereof;
- (25) A method for producing a compound of the formula:



wherein each symbol is as described in the above (1), or  
a salt thereof, which comprises subjecting a compound of  
5 the formula:



wherein each symbol is as described in the above (1), a  
salt or a reactive derivative thereof to a condensation  
reaction with a compound of the formula:



- compound as described in the above (1) or a salt thereof;
- (27) The composition as described in the above (26),  
which is a CC chemokine receptor (CCR) antagonist;
- (28) The pharmaceutical composition as described in the  
5 above (26), which is a CCR5 antagonist;
- (29) The composition as described in the above (26),  
which is for the treatment or prevention of infectious  
disease of HIV;
- (30) The composition as described in the above (26),  
10 which is for the treatment or prevention of AIDS;
- (31) The composition as described in the above (26),  
which is for the prevention of the progression of AIDS;
- (32) The composition as described in the above (29),  
which is used in combination with a protease inhibitor  
15 and/or a reverse transcriptase inhibitor;
- (33) The composition as described in the above (32),  
wherein the reverse transcriptase inhibitor is zidovudine,  
didanosine, zalcitabine, lamivudine, stavudine,  
nevirapine, delavirdine, efavirenz or abacavir;
- 20 (34) The composition as described in the above (32),  
wherein the protease inhibitor is saquinavir, ritonavir,  
indinavir or nelfinavir;
- (35) Use of the compound as described in the above (1) or  
a salt thereof in combination with a protease inhibitor  
25 and/or a reverse transcriptase inhibitor for the

10018321-121201

treatment or prebention of infectious diseases of HIV;  
 (36) A method for antagonizing a CC chemokine receptor  
 (CCR) in a mammal, which comprises administering an  
 effective amount of a compound described in the above (1)  
 or a salt thereof to a mammal;  
 (37) Use of a compound described in the above (1) or a  
 salt thereof in preparation of a medicament for  
 antagonizing a CC chemokine receptor (CCR); etc.

In the above formula(I), examples of the "5- to 6-  
 membered aromatic ring" of the "5- to 6-membered  
 aromatic ring which has a group of the formula:  $R-Z^1-X-Z^2$ -  
 wherein R is a hydrogen atom or an optionally substituted  
 hydrocarbon group, X is an optionally substituted  
 alkylene chain, and  $Z^1$  and  $Z^2$  are respectively hetero-  
 atoms, and which may have a further substituent"  
 represented by  $R^1$  include a 6-membered aromatic  
 hydrocarbon such as benzene, etc.; 5- to 6-membered  
 aromatic heterocyclic ring containing 1 to 4 hetero-atoms  
 consisting of 1 to 2 kinds of hetero-atoms selected from  
 oxygen atom, sulfur atom and nitrogen atom such as furan,  
 thiophene, pyrrole, imidazole, pyrazole, thiazole,  
 oxazole, isothiazole, isoxazole, tetrazole, pyridine,  
 pyrazine, pyrimidine, pyridazine, triazole, etc.; and the  
 like. Among others, benzene, furan, thiophene, pyridine,

Amen.


B3

10018334.1221001



etc. are preferable, benzene, furan or thiophene is more preferable, and in particular, benzene is preferable.

- Examples of the "hydrocarbon group" of the "optionally substituted hydrocarbon group" represented by R include (1) alkyl (e.g.,  $C_{1-10}$  alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower ( $C_{1-6}$ ) alkyl, etc., more preferable lower ( $C_{1-4}$ ) alkyl, etc.);
- (2) cycloalkyl (e.g.,  $C_{3-7}$  cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) alkenyl (e.g.,  $C_{2-10}$  alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower ( $C_{2-6}$ ) alkenyl, etc.);
- (4) cycloalkenyl (e.g.,  $C_{3-7}$  cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (5) alkynyl, (e.g.,  $C_{2-10}$  alkynyl, such as ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-pentylnyl, 3-hexynyl, etc., preferably lower ( $C_{2-6}$ ) alkynyl, etc.);
- (6) aralkyl (e.g., phenyl- $C_{1-4}$  alkyl (e.g., benzyl, phenethyl, etc.), etc.);
- (7) aryl (e.g., phenyl, naphthyl, etc.);
- (8) cycloalkyl-alkyl (e.g.,  $C_{3-7}$  cycloalkyl- $C_{1-4}$  alkyl such

*Ammon.*  
*B4* 

~~as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, etc.), and the like~~

Examples of the substituents, which the above-mentioned (1) alkyl, (2) cycloalkyl, (4) cycloalkenyl, 5 (5) alkynyl, (6) aralkyl, (7) aryl and (8) cycloalkyl-alkyl may have, include halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g., thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group 10 (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxy- 15 carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), 20 C<sub>1-4</sub> alkylenedioxy (e.g., -O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-O, etc.), optionally substituted sulfonamide [e.g., a group formed by binding of an optionally substituted amino group (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, 25 piperazine, piperidine, morpholine, thiomorpholine,

pyrrole, imidazole, etc.; etc.) to  $-\text{SO}_2-$ , formyl,  $\text{C}_{2-4}$  alkanoyl (e.g., acetyl, propionyl, etc.),  $\text{C}_{1-4}$  alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the "heterocyclic group" of the "optionally substituted heterocyclic group" as substituents of "optionally substituted hydrocarbon group" represented by R include a group formed by removing one hydrogen atom from aromatic heterocyclic ring or non-aromatic heterocyclic ring. Examples of the aromatic heterocyclic ring include 5- to 6-membered aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, oxadiazole, thiadiazole, etc. Examples of the non-aromatic heterocycle include 5- to 6-membered non-aromatic heterocycle containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from nitrogen atom, sulfur atom and oxygen atom, such as tetrahydrofuran, tetrahydrothiophene, dioxolane, dithiolane, oxathiolane, pyrrolidine, pyrroline, imidazolidine, imidazoline,

Ammon.  
B5

pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiazadine, morpholine, thiomorpholine, pyran and tetrahydropyran, as well as non-aromatic heterocycle in which a part or whole bond(s) of the aforementioned aromatic heterocycle is (are) a saturated bond, and the like (preferably, aromatic heterocycle such as pyrazole, thiazole, oxazole, tetrazole, etc.).

The "heterocyclic group" of the "optionally substituted heterocyclic group" as the substituent for the "optionally substituent hydrocarbon group" represented by R, may have 1 to 3 substituents at an optional replaceable position. Examples of such the substituent include halogen (e.g., fluorine, chlorine, bromine and iodine), nitro, cyano, a hydroxy group, an optionally substituted thiol group (e.g., thiol, C<sub>1-4</sub> alkylthio etc.), an optionally substituted amino group (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxycarbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl etc.), optionally halogenated C<sub>1-4</sub> alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), optionally

10018321-121201

halogenated C<sub>1-4</sub> alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), C<sub>1-4</sub> alkylenedioxy (e.g., -O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-O-, etc.), optionally substituted sulfonamide [e.g., an optionally substituted amino group (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.) binding to -SO<sub>2</sub>-], formyl, C<sub>2-4</sub> alkanoyl (e.g., acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc. (preferably, C<sub>1-4</sub> alkyl, etc.).

When the group of the formula: R-Z<sup>1</sup>-X-Z<sup>2</sup>- wherein each symbol is as defined above is a monovalent group, that is, it does not bind to the 5- to 6-membered aromatic ring to form a ring, as the group R, an optionally substituted alkyl group is preferable, an optionally halogenated lower alkyl group is more preferable, and in particular, an optionally halogenated C<sub>1-4</sub> alkyl group is preferable.

Examples of the "optionally substituted alkylene chain" represented by X include an optionally substituted straight or branched C<sub>1-6</sub> alkylene, etc. In said alkylene chain, a straight portion is preferably constituted by 1-4 carbon atoms, and in particular, an

10018321-121201

optionally substituted straight C<sub>1-4</sub> alkylene (preferably ethylene or propylene) is preferable as X.

Examples of the substituent, which the "alkylene chain" of the "optionally substituted alkylene chain" represented by X may have, include any one which can bind to a divalent chain constituting the straight portion, for example, C<sub>1-6</sub> lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.), lower (C<sub>3-7</sub>) cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.), formyl, lower (C<sub>2-7</sub>) alkanoyl (e.g., acetyl, propionyl, butyryl, etc.), an optionally esterified phosphono group, an optionally esterified carboxyl group, hydroxy group, oxo, etc., and more preferably C<sub>1-6</sub> lower alkyl (preferably C<sub>1-3</sub> alkyl), hydroxy group, oxo, etc.

Examples of the optionally esterified phosphono group include a group of the formula:  $P(O)(OR^7)(OR^8)$  wherein R<sup>7</sup> and R<sup>8</sup> are independently hydrogen, a C<sub>1-6</sub> alkyl group or a C<sub>3-7</sub> cycloalkyl group, and R<sup>7</sup> and R<sup>8</sup> may bind to each other to form a 5- to 7-membered ring.

In the above formula, examples of the C<sub>1-6</sub> alkyl group represented by R<sup>7</sup> and R<sup>8</sup> include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc., and examples

10048321-124201

of the C<sub>3-7</sub> cycloalkyl include cyclopropyl, cyclobutyl,  
 cyclopentyl, cyclohexyl, cycloheptyl, etc. Among others,  
 a straight C<sub>1-6</sub> lower alkyl is preferable and C<sub>1-3</sub> lower  
 alkyl is more preferable. The groups R<sup>7</sup> and R<sup>8</sup> may be the  
 same or different, and preferably the groups R<sup>7</sup> and R<sup>8</sup> are  
 the same. When R<sup>7</sup> and R<sup>8</sup> may bind to each other to form a  
 5- to 7-membered ring, the groups R<sup>7</sup> and R<sup>8</sup> bind to each  
 other to represent a straight C<sub>2-4</sub> alkylene chain of the  
 formula: -(CH<sub>2</sub>)<sub>2</sub>-, -(CH<sub>2</sub>)<sub>3</sub>-, -(CH<sub>2</sub>)<sub>4</sub>-, etc. Said chain may  
 have a substituent, and examples of the substituent  
 include hydroxy group, halogen, etc..

Examples of the optionally esterified carboxyl group  
 include a carboxyl group and an ester group formed by  
 binding a carboxyl group to a C<sub>1-6</sub> alkyl group or a C<sub>3-7</sub>  
 cycloalkyl group (e.g., methoxycarbonyl, ethoxycarbonyl,  
 propoxycarbonyl, isoprpxoxycarbonyl, butoxycarbonyl,  
 isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxy-  
 carbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.).

As the group X, an optionally substituted C<sub>1-4</sub>  
 alkylene is preferable, C<sub>1-4</sub> alkylene which may be  
 substituted with C<sub>1-3</sub> alkyl, hydroxy group or oxo is more  
 preferable, and in particular, a group of the formula: -  
 (CH<sub>2</sub>)<sub>n</sub>- (n is an integer of 1-4) is preferable.

Examples of the hetero-atom represented by Z<sup>1</sup> and Z<sup>2</sup>  
 include -O-, -S(O)<sub>m</sub>- (m is an integer of 0-2), -N(R<sup>4</sup>)- (R<sup>4</sup>

Amen.  
 B6

10048771-121201

Amen.  
 B7

is a hydrogen atom or an optionally substituted lower alkyl group), etc. As the group  $Z^1$ , -O- or  $-S(O)_m-$  (m is an integer of 0-2) is preferable, and -O- is more preferable. As the group  $Z^2$ , -O- or  $-N(R^4)-$  ( $R^4$  is a hydrogen atom or an optionally substituted lower alkyl group) is preferable, and -O- is more preferable.

Examples of the "optionally substituted lower alkyl group" represented by  $R^4$  include the same as the above "optionally substituted lower alkyl group" exemplified with respect to the "optionally substituted hydrocarbon group" represented by R.

Examples of the further substituent, which the "5- to 6-membered ring" of the "5- to 6-membered aromatic ring which has a group of the formula:  $R-Z^1-X-Z^2-$  wherein each symbol is as defined above, and which may have a further substituent" represented by  $R^1$  may have, in addition to the group of the formula:  $R-Z^1-X-Z^2-$ , include a halogen atom, nitro, cyano, an optionally substituted alkyl, an optionally substituted cycloalkyl, an optionally substituted hydroxy group, an optionally substituted thiol group (wherein a sulfur atom may be oxidized to form an optionally substituted sulfinyl group or an optionally substituted sulfonyl group), an optionally substituted amino group, an optionally substituted acyl group, an optionally esterified or



amidated carboxyl group, an optionally substituted aromatic group and the like.

Examples of the halogen as the substituents for R<sup>1</sup> include fluorine, chlorine, bromine, iodine, etc. Among  
5 others, fluorine and chlorine are preferable.

Examples of the alkyl in the optionally substituted alkyl as the substituents for R<sup>1</sup> include a straight or branched C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl  
10 isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., and preferably lower (C<sub>1-6</sub>) alkyl. Examples of the substituents in the optionally substituted alkyl include halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted  
15 thiol group (e.g., thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5-to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.;  
20 etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.),  
25 an optionally halogenated C<sub>1-4</sub> alkoxy-C<sub>1-4</sub> alkoxy (e.g.,

methoxymethoxy, methoxyethoxy, ethoxyethoxy,  
 trifluoromethoxyethoxy, trifluoroethoxyethoxy, etc.),  
 formyl, C<sub>2-4</sub> alkanoyl (e.g., acetyl, propionyl, etc.), C1-4  
 alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl,  
 5 etc.), etc., and the number of the substituents are  
 preferable 1 to 3.

Examples of the cycloalkyl in the optionally  
 substituted cycloalkyl as the substituents for R<sup>1</sup> include  
 C<sub>3-7</sub> cycloalkyl, etc. such as cyclopropyl, cyclobutyl,  
 10 cyclopentyl, cyclohexyl, cycloheptyl, etc. Examples of  
 the substituents in the optionally substituted cycloalkyl  
 include halogen (e.g., fluorine, chlorine, bromine,  
 iodine, etc.), nitro, cyano, hydroxy group, an optionally  
 substituted thiol group (e.g., thiol, C<sub>1-4</sub> alkylthio,  
 15 etc.), an optionally substituted amino group (e.g., amino,  
 mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered  
 cyclic amino such as tetrahydropyrrole, piperazine,  
 piperidine, morpholine, thiomorpholine, pyrrole,  
 imidazole, etc.; etc.), an optionally esterified or  
 20 amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxy-  
 carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub>  
 alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub>  
 alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an  
 optionally halogenated C<sub>1-4</sub> alkoxy (e.g., methoxy, ethoxy,  
 25 propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.),

Amen.  
 B8

1001834-1231001

formyl, C<sub>2-4</sub> alkanoyl (e.g., acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

5        Examples of the substituents in the optionally substituted hydroxy group as the substituents for R<sup>1</sup> include

10        (1) an optionally substituted alkyl (e.g., C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C<sub>1-6</sub>) alkyl, etc.);

15        (2) an optionally substituted cycloalkyl which may contain a hetero-atom (e.g., C<sub>3-7</sub> cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.; a saturated 5- to 6-membered heterocyclic ring group containing 1-2 hetero-atoms such as tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrothiopyranyl, etc.; etc., (preferably, tetrahydropyranyl, etc.));

20        (3) an optionally substituted alkenyl (e.g., C<sub>2-10</sub> alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C<sub>2-6</sub>) alkenyl, etc.);

25        (4) an optionally substituted cycloalkenyl (e.g. C<sub>3-7</sub>

cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);

(5) an optionally substituted aralkyl (e.g. phenyl- $C_{1-4}$  alkyl (e.g. benzyl, phenethyl, etc.), etc.);

(6) formyl or an optionally substituted acyl (e.g.  $C_{2-4}$  alkanoyl (e.g. acetyl, propionyl, butyryl, isobutyryl, etc.),  $C_{1-4}$  alkylsulfonyl (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc.);

(7) an optionally substituted aryl (e.g. phenyl, naphthyl, etc.); etc.

Examples of the substituents which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted cycloalkenyl, (5) optionally substituted aralkyl, (6) optionally substituted acyl and (7) optionally substituted aryl may have include halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g., thiol,  $C_{1-4}$  alkylthio, etc.), an optionally substituted amino group (e.g. amino; mono- $C_{1-4}$  alkylamino; di- $C_{1-4}$  alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an

optionally esterified or amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-6</sub> alkoxy (e.g., trifluoromethoxy, trifluoroethoxy, etc.; preferably an optionally halogenated C<sub>1-4</sub> alkoxy), formyl, C<sub>2-4</sub> alkanoyl (e.g., acetyl, propionyl, etc.), C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), an optionally substituted 5- to 6-membered aromatic heterocyclic ring [e.g., 5- to 6-membered aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as furan, thiophene, pyrrole, imidazole, pyrazole, thiazole, oxazole, isothiazole, isoxazole, tetrazole, pyridine, pyrazine, pyrimidine, pyridazine, triazole, etc.; examples of the substituents which said heterocyclic ring may have include halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, thiol group, amino group, carboxyl group, an optionally halogenated C<sub>1-4</sub> alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g.,

10018321-12201

acetyl, propionyl, etc.),  $C_{1-4}$  alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc.; and the number of the substituents are preferable 1 to 3.], etc., and the number of the substituents are preferably 1 to 3.

- 5        Examples of the substituents in the optionally substituted thiol group as the substituents for  $R^1$  are the same as the above-described substituents of the optionally substituted hydroxy group as the substituents for  $R^1$ , and among others,
- 10        (1) an optionally substituted alkyl (e.g.,  $C_{1-10}$  alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc. preferably lower ( $C_{1-6}$ ) alkyl, etc.);
- 15        (2) an optionally substituted cycloalkyl (e.g.,  $C_{3-7}$  cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) an optionally substituted aralkyl (e.g., phenyl- $C_{1-4}$  alkyl (e.g. benzyl, phenethyl, etc.), etc.);
- 20        (4) an optionally substituted aryl (e.g., phenyl, naphthyl, etc.); etc. are preferable.

      Examples of the substituents which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted aralkyl and (4) optionally substituted aryl

25

may have include halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g., thio, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group

5 (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxy-

10 carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.),

15 formyl, C<sub>2-4</sub> alkanoyl (e.g., acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the substituents of the optionally

20 substituted amino group as the substituents for R<sup>1</sup> include an amino group which may have the same one to two substituents as those of the above-described substituents of "the optionally substituted hydroxy group as the substituents for R<sup>1</sup>", etc. Among others,

25 (1) an optionally substituted alkyl (e.g., C<sub>1-10</sub> alkyl such

100183221-124201

- as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower ( $C_{1-6}$ ) alkyl, etc.);
- (2) an optionally substituted cycloalkyl (e.g.,  $C_{3-7}$  cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (3) an optionally substituted alkenyl (e.g.,  $C_{2-10}$  alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower ( $C_{2-6}$ ) alkenyl, etc.);
- (4) an optionally substituted cycloalkenyl (e.g.,  $C_{3-7}$  cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (5) formyl or an optionally substituted acyl (e.g.,  $C_{2-4}$  alkanoyl (e.g., acetyl, propionyl, butyryl, isobutyryl, etc.),  $C_{1-4}$  alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc.);
- (6) an optionally substituted aryl (e.g., phenyl, naphthyl, etc.); etc. are preferable.

Examples of the substituents, which each of the above-described (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl, (4) optionally substituted



cycloalkyl, (5) optionally substituted acyl and (6) optionally substituted aryl may have, include halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g., thiol,  $C_{1-4}$  alkylthio, etc.), an optionally substituted amino group (e.g., amino; mono- $C_{1-4}$  alkylamino; di- $C_{1-4}$  alkylamino; 5-to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl,  $C_{1-4}$  alkoxy-carbonyl, carbamoyl, mono- $C_{1-4}$  alkylcarbamoyl, di- $C_{1-4}$  alkylcarbamoyl, etc.), an optionally halogenated  $C_{1-4}$  alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated  $C_{1-4}$  alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl,  $C_{2-4}$  alkanoyl (e.g., acetyl, propionyl, etc.),  $C_{1-4}$  alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

The substituents in the optionally substituted amino group as the substituents for  $R^1$  may bind to each other to form a cyclic amino group (e.g., 5- to 6-membered cyclic amino, etc. such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole,

imidazole, etc.). Said cyclic amino group may have a substituent and examples of the substituents include halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), nitro cyano, hydroxy group, an optionally substituted thiol group (e.g., thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5-to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g., acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Examples of the optionally substituted acyl as the substituents for R<sup>1</sup> include

- (1) hydrogen;
- (2) an optionally substituted alkyl (e.g., C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl,

Amem.  
B9

sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, octyl, nonyl, decyl, etc., preferably lower ( $C_{1-6}$ ) alkyl, etc.);

(3) an optionally substituted cycloalkyl (e.g.,  $C_{3-7}$  cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);

(4) an optionally substituted alkenyl (e.g.,  $C_{2-10}$  alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower ( $C_{2-6}$ ) alkenyl, etc.);

(5) an optionally substituted cycloalkenyl (e.g.,  $C_{3-7}$  cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);

(6) an optionally substituted 5- to 6-membered monocyclic aromatic group (e.g., phenyl, 5- to 6-membered aromatic heterocyclic group (e.g., 5- to 6-membered aromatic heterocyclic group containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom, such as furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, tetrazolyl, pyridyl, pyrazyl, pirimidinyl, pyridazinyl, triazolyl, etc.);

(7) an optionally substituted 5- to 6-membered monocyclic non-aromatic heterocyclic group (e.g., a group which is formed by removing one hydrogen atom from a 5- to 6-

10018331.121201

membered monocyclic non-aromatic heterocycle containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from nitrogen atom, sulfur atom and nitrogen atom, such as tetrahydrofuran,

5 tetrahydrothiophene, dioxolane, dithiolane, oxathiolane, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, thiadiazine, morpholine, thiomorpholine, pyran, tetrahydropyran, etc.; preferably

10 dioxolanyl, etc) which is bound to a carbonyl group or a sulfonyl group (e.g., acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, butanoyl, octanoyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl,

15 cyclobutanecarbonyl, crotonyl, 2-cyclohexenecarbonyl, benzoyl, nicotinyl, methanesulfonyl, ethanesulfonyl, etc.). Examples of the substituents, which the above-mentioned (2) optionally substituted alkyl, (3) optionally substituted cycloalkyl, (4) optionally

20 substituted alkenyl, (5) optionally substituted cycloalkenyl, (6) optionally substituted 5- to 6-membered monocyclic aromatic group and (7) optionally substituted 5- to 6-membered monocyclic non-aromatic heterocycle may have, include halogen (e.g., fluorine, chlorine, bromine,

25 iodine, etc.), nitro, cyano, hydroxy group, an optionally

substituted thiol group (e.g., thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), C<sub>1-4</sub> alkylenedioxy (e.g., -O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-O-, etc.), optionally substituted sulfonamide [e.g., an optionally substituted amino group (e.g. amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.) which is bound to -SO<sub>2</sub>-, etc.], formyl, C<sub>2-4</sub> alkanoyl (e.g., acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3

Examples of the optionally esterified carboxyl group as the substituents for R<sup>1</sup> include

(1) hydrogen;

Amen.  
 B10

10018321 121201

- (2) an optionally substituted alkyl (e.g., C<sub>1-10</sub> alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C<sub>1-6</sub>) alkyl, etc.);
- (3) an optionally substituted cycloalkyl (e.g., C<sub>3-7</sub> cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);
- (4) an optionally substituted alkenyl (e.g., C<sub>2-10</sub> alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C<sub>2-6</sub>) alkenyl, etc.);
- (5) an optionally substituted cycloalkenyl (e.g., C<sub>3-7</sub> cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);
- (6) an optionally substituted aryl (e.g., phenyl, naphthyl, etc.); etc., and preferably carboxyl, lower (C<sub>1-6</sub>) alkoxycarbonyl, aryloxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, phenoxycarbonyl, naphthoxycarbonyl, etc.), etc.

Examples of the substituents, which the above-mentioned (2) optionally substituted alkyl, (3) optionally substituted cycloalkyl, (4) optionally substituted alkenyl, (5) optionally substituted cycloalkenyl and (6) optionally substituted aryl may have,

Ammon. B11

include halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g., thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an optionally halogenated C<sub>1-4</sub> alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C<sub>1-4</sub> alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g., acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substitutes are preferably 1 to 3.

Ammon. B12

Examples of the optionally amidated carboxyl group as the substitutes for R<sup>1</sup> include an carbonyl group binding to "an optionally substituted amino group", etc. which is the same as that of the above-described "optionally substituted amino group as the substituents for R<sup>1</sup>", and among others, carbamoyl, mono-C<sub>1-6</sub> alkylcarbamoyl, di-C<sub>1-6</sub> alkylcarbamoyl, etc. are

preferable.

Examples of the aromatic group in the optionally substituted aromatic group as the substituents for R<sup>1</sup> include 5- to 6-membered aromatic homocyclic or

5 heterocyclic ring such as phenyl, pyridyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, tetrazolyl, pyrazinyl pyrimidinyl, pyridazinyl, triazolyl, oxadiazolyl, thiadiazolyl, etc.; fused aromatic heterocyclic ring such

10 as benzofuran, indole, benzothiophene, benzoxazole, benzothiazole, indazole, benzimidazole, quinoline, isoquinoline, quinoxaline, phthalazine, quinazoline, cinnoline, etc.; etc. Examples of the substituents for these aromatic groups include halogen (e.g., fluorine,

15 chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g., thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered cyclic amino such as

20 tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), an

25 optionally halogenated C<sub>1-4</sub> alkyl (e.g., trifluoromethyl,



methyl, ethyl, etc.), an optionally halogenated  $C_{1-4}$   
 alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy,  
 trifluoromethoxy, trifluoroethoxy, etc.), formyl,  $C_{2-4}$   
 alkanoyl (e.g., acetyl, propionyl, etc.),  $C_{1-4}$   
 5 alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl,  
 etc.), etc., and the number of the substituents are  
 preferably 1 to 3.

The number of the above-mentioned substituents for  $R^1$   
 is 1-4 (preferably 1-2) and they may be the same or  
 10 different and present at any possible position on the  
 ring represented by  $R^1$ .

When the group represented by R binds to the 5- to  
 6-membered aromatic ring to form a ring, the group of the  
 formula:  $R-Z^1-X-Z^2$ - wherein each symbol is as defined  
 15 above (as the group R is preferably hydrogen atom) forms  
 a divalent group such as lower ( $C_{1-6}$ ) alkylenedioxy (e.g.,  
 $-O-CH_2-O-$ ,  $-O-CH_2-CH_2-O-$ ,  $-O-CH_2-CH_2-CH_2-O-$ , etc.), oxy-  
 lower ( $C_{1-6}$ ) alkylene-amino (e.g.,  $-O-CH_2-NH-$ ,  $-O-CH_2-CH_2-$   
 $NH-$ , etc.), oxy-lower ( $C_{1-6}$ ) alkylenethio (e.g.,  $-O-CH_2-S-$ ,  
 20  $-O-CH_2-CH_2-S-$ , etc.), lower ( $C_{1-6}$ ) alkylenediamino (e.g.,  $-$   
 $NH-CH_2-NH-$ ,  $-NH-CH_2-CH_2-NH-$ , etc.), thia-lower ( $C_{1-6}$ )  
 alkylene-amino (e.g.,  $-S-CH_2-NH-$ ,  $-S-CH_2-CH_2-NH-$ , etc.),  
 etc.

Preferred examples of the further substituent, which  
 25 the "5- to 6-membered ring" of the "5- to 6-membered

aromatic ring which has a group of the formula:  $R-Z^1-X-Z^2$ ,  
 wherein each symbol is as defined above, and which may  
 have a further substituent" represented by  $R^1$  may have,  
 in addition to the group of the formula:  $R-Z^1-X-Z^2$ ,

5 include, in particular, a lower ( $C_{1-4}$ ) alkyl optionally  
 substituted with a halogen or a lower ( $C_{1-4}$ ) alkoxy (e.g.,  
 methyl, ethyl, t-butyl, trifluoromethyl, methoxymethyl,  
 ethoxymethyl, propoxymethyl, butoxymethyl, methoxyethyl,  
 ethoxyethoxy, propoxyethyl, butoxyethyl, etc.), a lower  
 10 ( $C_{1-4}$ ) alkoxy optionally substituted with a halogen or a  
 lower ( $C_{1-4}$ ) alkoxy (e.g., methoxy, ethoxy, propoxy,  
 butoxy, t-butoxy, trifluoromethoxy, methoxymethoxy,  
 ethoxymethoxy, propoxymethoxy, butoxymethoxy,  
 methoxyethoxy, ethoxyethoxy, propoxyethoxy, butoxyethoxy,  
 15 methoxypropoxy, ethoxypropoxy, propoxypropoxy,  
 butoxypropoxy, etc.), halogen (e.g., fluorine, chlorine,  
 etc.), nitro, cyano, an amino group optionally  
 substituted with 1-2 lower ( $C_{1-4}$ ) alkyl groups, formyl  
 group or lower ( $C_{2-4}$ ) alkanoyl groups (e.g., amino,  
 20 methylamino, dimethylamino, formylamino, acethylamino,  
 etc.), 5- to 6-membered cyclic amino (e.g., 1-  
 pyrrolidinyl, 1-piperazinyl, 1-piperidinyl, 4-morpholino,  
 4-thiomorpholino, 1-imidazolyl, 4-tetrahydropyranyl,  
 etc.), etc.

25 When  $R^1$  is a benzene, the "group of the formula:  $R$ -

Ames.  
 B13

1001321.121201

10018324-121204  
T02T21-T2E1001

$Z^1-X-Z^2-$  is preferably present at para position and the further substituent, which the "5- to 6-membered aromatic ring which may have, in addition to the group of the formula:  $R-Z^1-X-Z^2-$  is preferably present at meta position.

In the above formula, examples of the "optionally substituted imino group" represent by Y include a divalent group of the formula:  $-N(R^5)-$  wherein  $R^5$  is hydrogen atom or a substituent, etc.

10 As  $R^5$ , hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted thiol group (the sulfur atom may be oxidized to form an optionally substituted sulfinyl group or an optionally substituted sulfonyl group), an 15 optionally substituted amino group, an optionally esterified or amidated carboxyl group, and an optionally substituted acyl group, etc. are preferable, and hydrogen atom, an optionally substituted hydrocarbon group, an 20 optionally substituted heterocyclic group and an optionally substituted acyl group, etc. are more preferable.

As the preferable  $R^5$ , hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted acyl group, etc. are preferable,  $C_{1-4}$  alkyl,  $C_{1-4}$  25

alkylsulfonyl, formyl, C<sub>2-5</sub> alkanoyl etc. are more preferable, C<sub>1-4</sub> alkyl, formyl, C<sub>2-5</sub> alkanoyl etc. are further more preferable, and in particular, formyl or ethyl is preferable. As other preferably R<sup>5</sup>, there is a group represented by the formula  $-(CH_2)_k-R^6$  [wherein k represents 0 or 1, R<sup>6</sup> represents an optionally substituted 5- to 6-membered monocyclic aromatic group (similar to "(6) an optionally substituted 5- to 6-membered monocyclic aromatic group" exemplified with respect to an optionally substituted acyl group as the substituent for R<sup>1</sup>; preferably phenyl, pyrazolyl, thiazolyl, oxazolyl, tetrazolyl, etc., each being optionally substituent with halogen, optionally halogenated C<sub>1-4</sub> alkyl, optionally halogenated C<sub>1-4</sub> alkoxy, etc.)].

Example of the "optionally substituted hydrocarbon group" as R<sup>5</sup> are the same as the "optionally substituted hydrocarbon group" of R. Examples of the "optionally substituted heterocyclic group" as R<sup>5</sup> include the same "optionally substituted heterocyclic group" as the substituent for the "optionally substituted hydrocarbon group" represented by R, and examples of the "optionally substituted hydroxy group", the "optionally substituted thiol group", the "optionally substituted amino group", the "optionally esterified or amidated carboxyl group"

and the "optionally substituted acyl group" as  $R^5$  include the same "optionally substituted hydroxy group",

"optionally substituted thiol group", "optionally substituted amino group", "optionally esterified or  
5 amidated carboxyl group" and "optionally substituted acyl group" as the substituent for  $R^1$ .

In the above formula (I), examples of the

"optionally substituted aliphatic hydrocarbon group"

(aliphatic straight chain hydrocarbon group and aliphatic  
10 cyclic hydrocarbon group) represented by  $R^2$  and  $R^3$  include  
(1) an optionally substituted alkyl (e.g.,  $C_{1-10}$  alkyl such  
as methyl, ethyl, propyl, isopropyl, butyl, isobutyl,  
sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl,  
hexyl, heptyl, octyl, nonyl, decyl, etc., preferably  
15 lower ( $C_{1-6}$ ) alkyl, etc.);

(2) an optionally substituted cycloalkyl (e.g.,  $C_{3-8}$   
cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl,  
cyclohexyl, cycloheptyl, cyclooctyl, etc.; etc.),  
provided that

20 (2-1) said cycloalkyl may contain one hetero-atom  
selected from a sulfur atom, an oxygen atom and a  
nitrogen atom to form oxirane, thiorane, aziridine,  
tetrahydrofuran, tetrahydrothiophene, pyrrolidine,  
tetrahydropyran, tetrahydrothiopyran, tetrahydrothiopyran  
25 1-oxide, piperidine, etc. (preferably, 6-membered ring

Amen.  
B14

1003821-124201

such as tetrahydropyran, tetrahydrothiopyran, piperidine, etc.); that

(2-2) said cycloalkyl may be fused with a benzene ring to form indane, tetrahydronaphthalene, etc. (preferably, indane, etc.); and that

(2-3) said cycloalkyl may have a bridging through a straight chain constituted by 1-2 carbon atoms to form a bridged hydrocarbon residue such as bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, etc., preferably, a cyclohexyl group, etc. having a bridging through a straight chain constituted by 1-2 carbon atoms, and more preferably bicycle[2.2.1]heptyl, etc.;

(3) an optionally substituted alkenyl (e.g., C<sub>2-10</sub> alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl etc., preferably lower (C<sub>2-6</sub>)alkenyl, etc.);

(4) an optionally substituted cycloalkenyl (e.g., C<sub>3-7</sub> cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.); etc.

Examples of the substituents, which the above-mentioned (1) optionally substituted alkyl, (2) optionally substituted cycloalkyl, (3) optionally substituted alkenyl and (4) optionally substituted cycloalkenyl may have, include halogen (e.g., fluorine,

chlorine, bromine, iodine, etc.), an optionally halogenated lower (C<sub>1-4</sub>) alkyl, an optionally halogenated lower C<sub>1-4</sub> alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), C<sub>1-4</sub> alkylenedioxy (e.g., -O-CH<sub>2</sub>-O-, -O-CH<sub>2</sub>-CH<sub>2</sub>-O-, etc.), formyl, C<sub>2-4</sub> alkanoyl (e.g., acetyl, propionyl, etc.), C<sub>1-4</sub> alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), phenyl-lower (C<sub>1-4</sub>) alkyl, C<sub>3-7</sub> cycloalkyl, cyano, nitro, hydroxy group, an optionally substituted thiol group (e.g., thiol, C<sub>1-4</sub> alkylthio, etc.), an optionally substituted amino group (e.g., amino; mono-C<sub>1-4</sub> alkylamino; di-C<sub>1-4</sub> alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub> alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub> alkylcarbamoyl, di-C<sub>1-4</sub> alkylcarbamoyl, etc.), a lower (C<sub>1-4</sub>) alkoxy-carbamoyl, oxo group (preferably, halogen, an optionally halogenated lower (C<sub>1-4</sub>) alkyl, an optionally halogenated lower (C<sub>1-4</sub>) alkoxy, phenyl-lower (C<sub>1-4</sub>) alkyl, C<sub>3-7</sub> cycloalkyl, cyano, hydroxy group, etc.), etc., and the number of the substituents are preferably 1 to 3.

Preferred examples of the "optionally substituted aliphatic hydrocarbon group" represented by R<sup>2</sup> and R<sup>3</sup>

include (1) a lower ( $C_{1-6}$ ) straight or branched alkyl which may have 1-3 substituents selected from the class consisting of halogen, cyano, hydroxy group and  $C_{3-7}$  cycloalkyl;

- 5 (2)  $C_{5-8}$  cycloalkyl which may be substituted with 1-3 substituents selected from the class consisting of a halogen, an optionally halogenated lower ( $C_{1-4}$ ) alkyl and a phenyl-lower ( $C_{1-4}$ ) alkyl, which may contain a hetero-atom selected from the class consisting of a sulfur atom,
- 10 an oxygen atom and a nitrogen atom, which may be fused with a benzene ring and which may have a bridging through a  $C_{1-2}$  straight chain (e.g., cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, tetrahydropyranyl, tetrahydrothiapyranyl, piperidinyl, indanyl,
- 15 tetrahydronaphthalenyl, piperidinyl, indanyl, tetrahydronaphthalenyl, bicyclo[2.2.1]heptyl, etc., each of which may be substituted); etc.

In the above formula (I), example of the "optionally substituted alicyclic (non-aromatic)

20 heterocyclic group" represented by  $R^2$  and  $R^3$  include 5- to 6-membered non-aromatic heterocyclic ring containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom such as tetrahydrofuran, tetrahydrothiophene,

25 dioxolane, dithiolane, oxathiolane, pyrrolidine,



pyrroline, imidazolidine, imidazoline, pyrazolidine,  
 pyrazoline, piperidine, piperazine, oxazine, oxadiazine,  
 thiazine, thiadiazine, morpholine, thiomorpholine, pyran,  
 tetrahydropyran etc. Among others, a 5- to 6-membered  
 5 non-aromatic heterocyclic ring containing 1 hetero-atom  
 such as tetrahydrofuran, piperidine, tetrahydropyran,  
 tetrahydrothiopyran, etc. and so on are preferable.

Examples of the substituent, which the "alicyclic  
 heterocyclic group" in the "optionally substituted  
 10 alicyclic heterocyclic group" represented by  $R^2$  and  $R^3$   
 may have, include halogen (e.g., fluorine, chlorine,  
 bromine, iodine, etc.), an optionally halogenated lower  
 ( $C_{1-4}$ ) alkyl, an optionally halogenated  $C_{1-4}$  alkoxy (e.g.,  
 methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy,  
 15 trifluoroethoxy, etc.),  $C_{1-4}$ alkylenedioxy (e.g.,  $-O-CH_2-O-$ ,  
 $-O-CH_2-CH_2-O-$ , etc.), formyl,  $C_{2-4}$ alkanoyl (e.g., acetyl,  
 propionyl, etc.),  $C_{1-4}$ alkylsulfonyl (e.g., methanesulfonyl,  
 ethanesulfonyl, etc.), phenyl-lower( $C_{1-4}$ )alkyl,  $C_{3-7}$   
 cycloalkyl, cyano, nitro, hydroxy group, an optionally  
 20 substituted thiol group (e.g., thiol,  $C_{1-4}$  alkylthio,  
 etc.), an optionally substituted amino group (e.g. amino;  
 mono- $C_{1-4}$  alkylamino; di- $C_{1-4}$ alkylamino; 5- to 6-membered  
 cyclic amino such as tetrahydropyrrole, piperazine,  
 piperidine, morpholine, thiomorpholine, pyrrole,  
 25 imidazole, etc.; etc.), an optionally esterified or

10018324-121204

amidated carboxyl group (e.g., carboxyl, C<sub>1-4</sub>alkoxy-carbonyl, carbamoyl, mono-C<sub>1-4</sub>alkylcarbamoyl, di-C<sub>1-4</sub>alkylcarbamoyl, etc.), a lower (C<sub>1-4</sub>) alkoxy-carbonyl, oxo group (preferably, halogen, an optionally halogenated lower (C<sub>1-4</sub>) alkyl, an optionally halogenated lower (C<sub>1-4</sub>) alkoxy, phenyl-lower (C<sub>1-4</sub>) alkyl, C<sub>3-7</sub> cycloalkyl, cyano, hydroxy group, etc.), etc., and the number of the substituents are preferably 1 to 3.

Among others, as R<sup>2</sup>, an optionally substituted acyclic hydrocarbon group (e.g., alkyl, alkenyl, etc., each of which may be substituted) is preferable, an optionally substituted lower C<sub>1-6</sub> alkyl group is more preferable, and in particular, an optionally substituted methyl group is preferable.

As R<sup>3</sup>, an optionally substituted alicyclic hydrocarbon group (e.g., cycloalkyl, cycloalkenyl, etc., each of which may be substituted; preferably, an optionally substituted lower C<sub>3-8</sub> cycloalkyl group; and more preferably, an optionally substituted cyclohexyl) or an optionally substituted alicyclic heterocyclic group (preferably, an optionally substituted saturated alicyclic heterocyclic group (preferably, 6-membered ring group); more preferably, an optionally substituted tetrahydropyranyl, an optionally substituted tetrahydrothiopyranyl or an optionally substituted

piperidyl; an in particular, an optionally substituted tetrahydropyranyl) is preferable.

As the compound represented by the above formula (I),

- 7-(4-ethoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-
- 5 (tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 1-ethyl-7-(4-propoxyethoxyphenyl)-N-[4-[[N-methyl-N-
- (tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 10 7-(4-butoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-
- (tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 7-(4-ethoxythoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-
- (tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-
- 15 benzazepine-4-carboxamide,
- 1-formyl-7-(4-propoxyethoxyphenyl)-N-[4-[[N-methyl-N-
- (tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 7-(4-butoxyethoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-
- 20 (tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,
- 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-
- (tetrahydropyran-5-yl)amino]methyl]phenyl]-1-propyl-2,3-dihydro-1-benzazepine-4-carboxamide,
- 25 N-[4-[[N-methyl-N-(tetrahydropyran-5-

Amen  
B15

10018321.121201

- yl) amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-1-propyl-2,3-dihydro-1-benzazepine-4-carboxamide,  
 1-benzyl-7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl) amino]methyl]phenyl]-2,3-dihydro-1-  
 5 benzazepine-4-carboxamide,  
 7-(4-butoxyethoxyphenyl)-1-cyclopropylmethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl) amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,  
 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl) amino]methyl]phenyl]-1-phenyl-2,3-  
 10 dihydro-1-benzazepine-4-carboxamide,  
 7-(4-butoxyethoxyphenyl)-1-(3,4-methylenedioxy)phenyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl) amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-  
 15 carboxamide,  
 7-(4-butoxyethoxyphenyl)-1-(2-methyloxazol-5-yl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl) amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,  
 1-allyl-7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl) amino]methyl]phenyl]-2,3-dihydro-1-  
 20 benzazepine-4-carboxamide,  
 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl) amino]methyl]phenyl]-1-(3-thienyl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide,  
 25 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-

- (tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(thiazol-2-yl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide,  
 7-(4-butoxyethoxyphenyl)-1-(1-methylpyrazol-4-yl)methyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,  
 7-(4-butoxyethoxyphenyl)-1-(3-methylisothiazol-4-yl)methyl-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,  
 7-(4-butoxyethoxyphenyl)-1-(1-ethylpyrazol-4-yl)methyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,  
 7-(4-butoxyethoxyphenyl)-1-isobutyl-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide,  
 1-isobutyl-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxamide,  
 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(thiazol-5-yl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide,  
 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(1-

methylnitrazol-5-yl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide,  
7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(2-methylnitrazol-5-yl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide etc. are preferable.

Examples of the salts of the compound represented by the formula (I) include a pharmaceutically acceptable salt such as a salt with inorganic base, a salt with organic base, a salt with inorganic acid, a salt with organic acid, a salt with basic or acidic amino acid, etc. Suitable examples of the salt with the inorganic base include a salt with alkali metal (e.g. sodium, potassium, etc.), alkaline earth metal (e.g. calcium, magnesium, etc.), aluminum, ammonium, etc. Suitable examples of the salt with the organic base include a salt with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N'-dibenzylethylenediamine, etc. Suitable examples of the salt with the inorganic acid include a salt with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc. Suitable examples of the salt with the organic acid include a salt with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric

acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc. Suitable examples of the salt with the basic amino acid include a salt with arginine, lysine, ornithine, etc. Suitable examples of the salt with the acidic amino acid include a salt with aspartic acid, glutamic acid, etc. The compound of the formula (I) of the present invention may be hydrated or non-hydrated. When the compound of the formula (I) of the present invention exists as configuration isomer, diastereomer, conformer, etc., it is possible to isolate individual isomers with a per se known separation and purification method, if desired. When the compound of the formula (I) of the present invention is racemate, it can be separated into (S)-isomer and (R)-isomer with usual optical resolution and individual optical isomers and a mixture thereof are included in the scope of the present invention.

The pro-drug of the compound of the formula (I) or a salt thereof of the present invention [hereinafter, referred to as Compound (I) in some cases] means a compound which is converted to Compound (I) under the physiological condition or with a reaction due to an enzyme, an gastric acid, etc. in the living body, that is, a compound which is converted to Compound (I) with

oxidation, reduction, hydrolysis, etc. according to an enzyme; a compound which is converted to Compound (I) with hydrolysis by gastric acid, etc.; etc. Examples of the pro-drug of Compound (I) include a compound wherein an amino group of Compound (I) is substituted with acyl, alkyl, phosphoric acid, etc. (e.g. a compound wherein an amino group of Compound (I) is substituted with eicosanyl, alanyl, pentylaminocarbonyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonyl, tetrahydrofuranyl, pyrrolidylmethyl, pivaloyloxymethyl, tert-butyl, etc.); a compound wherein a hydroxy group of Compound (I) is substituted with acyl, alkyl, phosphoric acid, boric acid, etc. (e.g. a compound wherein a hydroxy group of Compound (I) is modified with acetyl, palmitoyl, propanoyl, pivaloyl, succinyl, fumaryl, alanyl, dimethylaminomethylcarbonyl, etc.); a compound wherein a carboxyl group of Compound (I) is modified with ester, amide, etc. (e.g. a compound wherein a carboxyl group of Compound (I) is modified with ethyl ester, phenyl ester, carboxymethyl ester, dimethylaminomethyl ester, pivaloyloxymethyl ester, ethoxycarbonyloxyethyl ester, phthalidyl ester, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl ester, cyclohexyloxycarbonylethyl ester, methyl amide, etc.); etc. These pro-drugs can be produced by per se known method from Compound (I).



The pro-drug of Compound (I) may be a compound which is converted into Compound (I) under the physiological conditions as described in "Pharmaceutical Research and Development", Vol.7 (Drug Design), pages 163-198 published in 1990 by Hirokawa Publishing Co.

Compound (I) may be labeled with isotope (e.g.  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{35}\text{S}$ ,  $^{125}\text{I}$ , etc), etc.

The present compound of the formula (I) or a salt thereof alone or as an admixture with a pharmaceutically acceptable carrier (e.g. solid formulations such as tablets, capsules, granules, powders, etc.; liquid formulations such as syrups, injections, etc.) may be orally or non-orally (preferably orally) administered.

Examples of non-oral formulations include injections, drops, suppositories, pessaries, etc. In particular, pessary is useful for the prevention of infectious diseases of HIV.

Examples of the carriers include various organic or inorganic carriers which are generally used in this field. For example, an excipient, a lubricant, a binder, a disintegrating agent, etc. are used in solid formulations, and a solvent, a solubilizer, a suspending agent, an isotonicizing agent, a buffer, a soothing agent, etc. are used in liquid formulations. In addition, if desired, an appropriate additive such as a preservative, an

*Amen*  
*B16*

antioxidant, a colorant, a sweetener, etc. may be used. Suitable examples of the excipient include lactose, sucrose, D-mannitol, starch, crystalline cellulose, light silicic acid anhydride, etc. Suitable examples of the

5 lubricant include magnesium stearate, calcium stearate, talc, colloidal silica, etc. Suitable examples of the binder include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl-pyrrolidone, etc. Suitable examples

10 of the disintegrating agent include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, sodium carboxymethyl starch, etc. Suitable examples of the solvent include water for injection, alcohol, propylene glycol, macrogol, sesame

15 oil, corn oil, etc. Suitable examples of the solubilizer include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc. Suitable examples of the suspending agent include

20 surfactants such as stearyl triethanolamine, sodium laurylsulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzetonium chloride, glycerin monostearate, etc.; hydrophilic polymers such as polyvinylalcohol, polyvinylpyrrolidone, sodium

25 carboxymethyl cellulose, methyl cellulose, hydroxymethyl

10018321.121201

cellulose hydroxyethyl cellulose, hydroxypropyl cellulose,  
 etc. Suitable examples of the isotonizing agent include  
 sodium chloride, glycerin, D-mannitol, etc. Suitable  
 examples of the buffer include a buffer solution of  
 5 phosphate, acetate, carbonate, citrate, etc. Suitable  
 examples of the soothing agent include benzylalcohol, etc.  
 Suitable examples of the preservative include  
 paraoxybenzoic acid esters, chlorobutanol, benzylalcohol  
 phenethylalcohol, dehydroacetic acid, sorbic acid, etc.  
 10 Suitable examples of the antioxidant include sulfites,  
 ascorbic acid, etc.

The present invention further provides production  
 methods of the compound of the formula (I) or a salt  
 thereof.

15 The compound of the formula (I) or a salt thereof  
 can be produced in accordance with per se known methods,  
 for example, the methods described in JP-A-73476/1996, or  
 analogous methods thereto, etc.

A salt of the compound of the formulas (II), (III),  
 20 (IV), (V), (I-1) and (I-2) (hereinafter, abbreviated as  
 Compound(II), Compound(III), Compound(IV), Compound(V),  
 Compound(I-1) and Compound(I-2), respectively, in some  
 cases) may be similar to that of Compound (I).

In the following reactions, when the starting  
 25 compounds have, as substituents, amino group, carboxyl

Amen.  
 B17

10013321-121201

group and/or hydroxy group, these groups may be protected by conventional protective groups such as those generally employed in peptide chemistry, etc. After the reaction, if necessary, the protective groups may be removed to  
5 obtain the desired compound.

Examples of an amino-protective group include an optionally substituted C<sub>1-6</sub> alkylcarbonyl (e.g., acetyl, propionyl, etc.), formyl, phenylcarbonyl, C<sub>1-6</sub> alkyloxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, 10 t-butoxycarbonyl, etc.), phenyloxycarbonyl (e.g., benzoxycarbonyl, etc.), C<sub>7-10</sub> aralkyloxycarbonyl (e.g., benzyloxycarbonyl, etc.), trityl, phthaloyl, etc. These protective groups may be substituted by 1 to 3 substituents such as halogen atom (e.g., fluorine, 15 chlorine, bromine, iodine, etc.), C<sub>1-6</sub> alkylcarbonyl (e.g., acetyl, propionyl, butyryl, etc.), nitro group, etc.

Examples of a carboxyl-protective group include an optionally substituted C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, 20 trityl, silyl, etc. These protective groups may be substituted by 1 to 3 substituents such as halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), C<sub>1-6</sub> alkylcarbonyl (e.g., acetyl, propionyl, butyryl, etc.), formyl, nitro group, etc.

25 Examples of a hydroxy-protective group include an

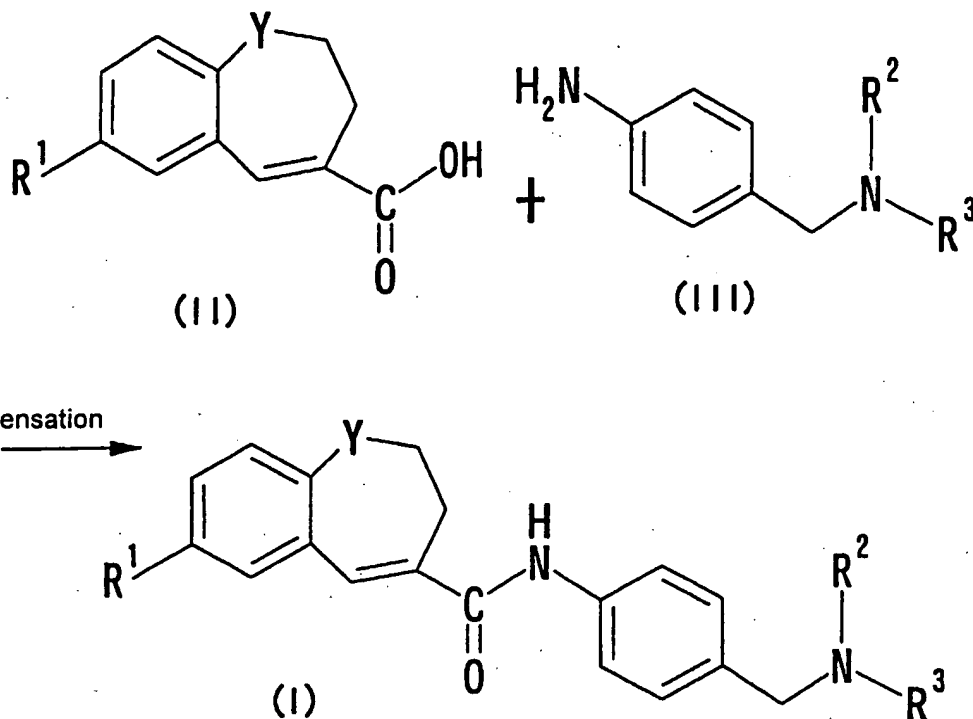
optionally substituted C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, C<sub>7-10</sub> aralkyl (e.g., benzyl, etc.), C<sub>1-6</sub> alkylcarbonyl (e.g., acetyl, propionyl, etc.), formyl, phenyloxycarbonyl, C<sub>7-10</sub> aralkyloxycarbonyl (e.g., benzyloxycarbonyl, etc.), pyranlyl, furanyl, silyl, etc. These protective groups may be substituted by 1 to 4 substituents such as halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), C<sub>1-6</sub> alkyl, phenyl, C<sub>7-10</sub> aralkyl, nitro group, etc.

10        These protective group may be introduced or removed by per se known methods (e.g. a method described in Protective Groups in Organic Chemistry (J.F.W. McOmie et al.; Plenum Press Inc.). For example, employable method for removing the protective groups is a method using an

15        acid, a base, reduction, ultraviolet ray, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, etc.

[Method A]

1001833-121201



wherein each symbol is as defined above.

This production method is carried out by reacting Compound (II) with Compound (III) to obtain the anilide Compound (I).

The condensation reaction of Compounds (II) and (III) is carried out by usual methods for peptide synthesis. Said methods for peptide synthesis are employed according to optional known methods, for example, methods described in "Peptide Synthesis" written by M. Bodansky and M. A. Ondetti, Interscience, New York, 1966; "The Proteins", volume 2, written by F. M. Finn and K. Hofmann, H. Nenrath and R. L. Hill edition,

Academic Press Inc., New York, 1976; "peputido-gosei no kiso to jikken (Basis and Experiment of Peptide Synthesis)" written by Nobuo Izumiya et al., Maruzen K.K., 1985; etc., as well as azide method, chloride method, acid anhydride method, mixed acid anhydride method, DCC method, active ester method, method using Woodward reagent K, carbonyldiimidazole method, oxidation-reduction method, DCC/HONB method, etc. and in addition WSC method, method using diethyl cyanophosphate (DEPC), etc. The condensation reaction can be carried out in a solvent.

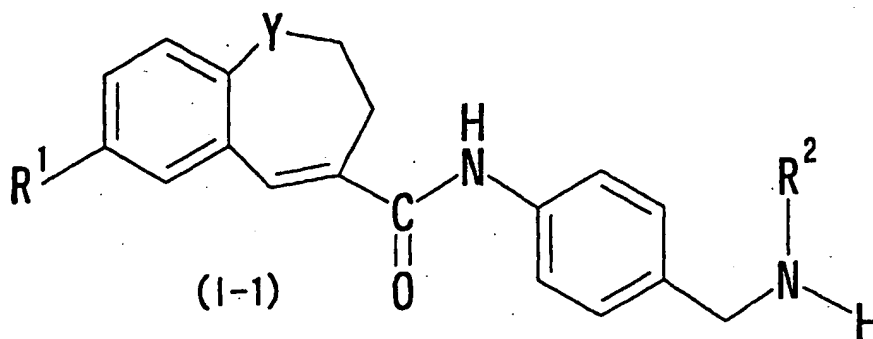
Examples of the solvents to be employed in the reaction include anhydrous or hydrous N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine, chloroform, dichloromethane, tetrahydrofuran (THF), dioxane, acetonitrile, or a suitable mixture of these solvents.

Usually, about 1-2 moles of the Compound (III) are used per 1 mole of the Compound (II). The reaction temperature is generally about  $-20^{\circ}\text{C}$  to about  $50^{\circ}\text{C}$ , preferably about  $-10^{\circ}\text{C}$  to about  $30^{\circ}\text{C}$  and the reaction time is generally about 1 to about 100 hours, preferably about 2 to about 40 hours. The thus obtained anilide derivative (I) can be isolated and purified by known separation and purification methods such as concentration,

concentration under reduced pressure, extraction, crystallization, recrystallization, solvent convert, chromatography, etc.

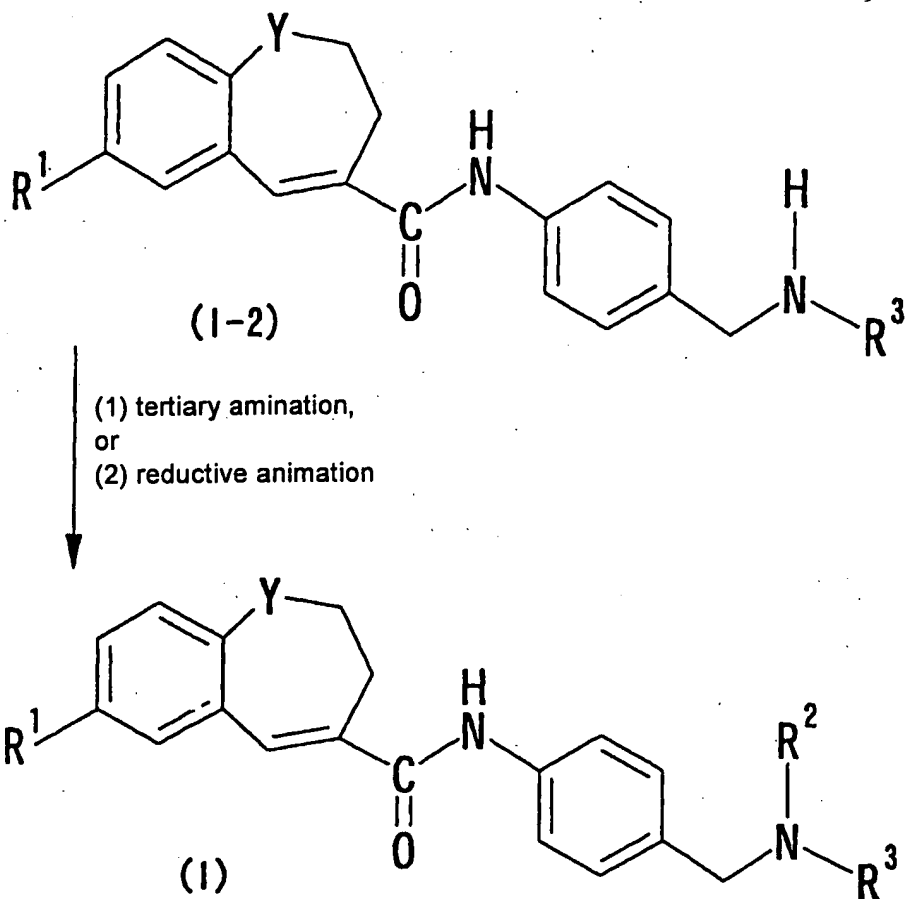
In addition, the compound of the formula (II) or a salt thereof is a novel compound and useful as an intermediate for producing the compound of the formula (I) or a salt thereof.

[Method B]



or





5 (1) Compound (I) can be produced by reacting Compound (I-1) or (I-2) with halogenated alkyl or halogenated aralkyl. Examples of a halogen atom include chlorine, bromine, iodine, etc. and usually about 1 to 2 moles of the halogenated alkyl or halogenated aralkyl is used per mole of Compound (I-1) or (I-2). If necessary, the reaction smoothly proceeds by addition of about once to thrice moles of a base such as triethylamine,

10 diisopropylethylamine, pyridine, lithium hydride, sodium

Amen  
 B18

10018324.121201

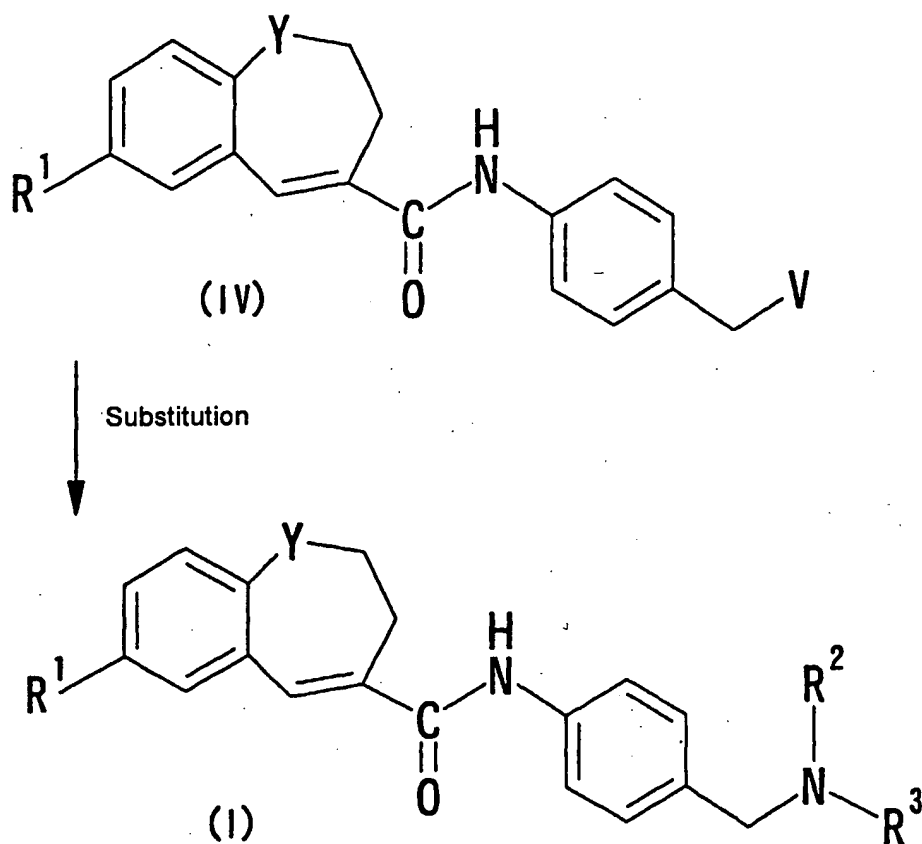
hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and further sodium iodide, potassium iodide, etc.

5 This tertiary amination reaction is carried out in an inert solvent such as methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethyl ether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO),  
10 pyridine, etc., or a mixture of these solvents. The reaction temperature is generally about 0°C to 180°C, and the reaction time is generally about 1 hour to about 40 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

15 (2) Compound (I) having a tertiary amino can be produced by reacting Compound (I-1) or (I-2) with an aldehyde compound in the presence of a reductive amination reagent such as triacetoxysodium borohydride, sodium cyanoborohydride, sodium borohydride, etc. The  
20 conditions of this reductive amination reaction vary depending on the reagent to be used. For example, when sodium triacetoxyborohydride is used, reaction is carried out in an inert solvent such as dichloromethane, chloroform, 1,2-dichloroethane, tetrahydrofuran, diethyl  
25 ether, dioxane, acetonitrile, dimethylformamide (DMF),


etc., or a mixture of these solvents. In this case, about 1 to 2 moles of the reagent is used per mole of Compound (I-1) or (I-2). The reaction temperature is generally about 0°C to about 80°C, and the reaction time is generally about 1 hour to about 40 hours. This reaction is preferably carried out under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

[Method C]



wherein  $V$  in the Compound (IV) is a halogen atom (chlorine, bromine, iodine, etc.), or a sulfonyloxy group

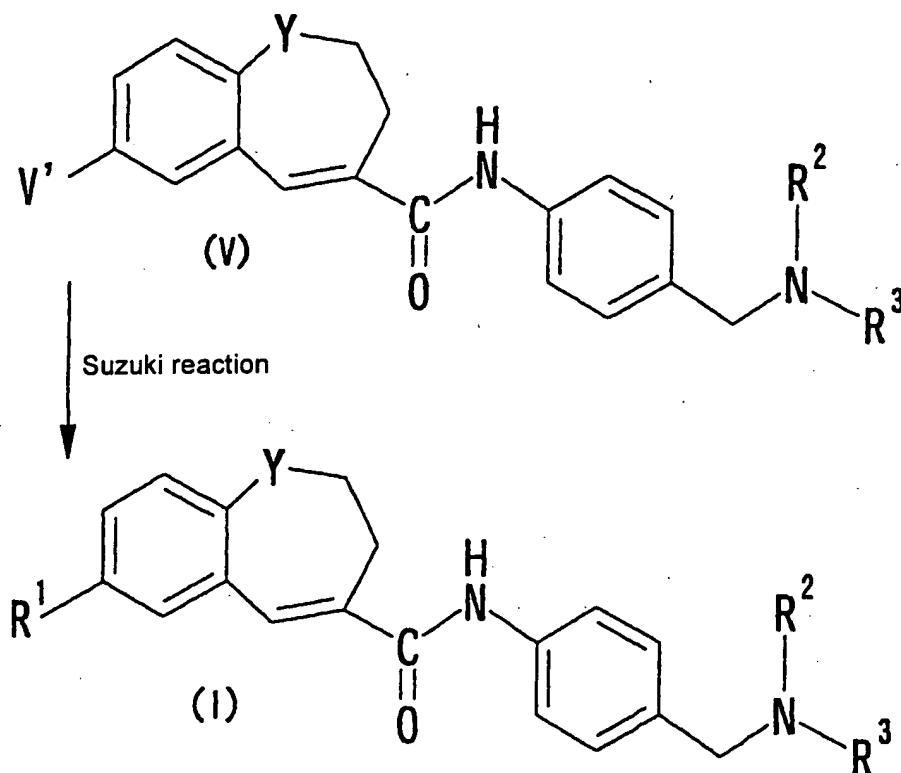
(methanesulfonyloxy group, trifluoromethanesulfonyloxy group, benzenesulfonyloxy group, toluenesulfonyloxy group, etc.), and the other symbols are as defined above.

*Amer. B 19* 

Compound (I) having a tertiary amino group can be produced by reacting Compound (IV) and a secondary amine compound. Usually, about 1 to 3 moles of the secondary amine compound is used per mole of Compound (IV). If necessary, the reaction smoothly proceeds by addition of about once to thrice moles of a base such as

triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and further sodium iodide, potassium iodide, etc. This substitution reaction is carried out in an inert solvent such as methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethyl ether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine, etc., or a mixture of these solvents. The reaction temperature is generally about -10°C to about 180°C, and the reaction time is generally about 1 hour to about 40 hours. The reaction is carried out preferably under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

[Method D]



wherein V' in Compound (V) is a halogen atom (bromine, iodine, etc.) or a sulfonyloxy group (trifluoromethanesulfonyloxy group, etc.), and the other symbols are as defined above.

Compound (I) wherein the group R<sup>1</sup> is a 5- to 6-membered aromatic ring group can be produced by subjecting Compound (V) to, for example, Suzuki reaction [cross condensation reaction of aryl borate with e.g. aryl halide or aryloxytrifluoromethane-sulfonate in the presence of a palladium catalyst; A. Suzuki et al., Synth. Commun. 1981, 111, 513]. Usually, about 1-1.5 times moles of aryl borate is used per mole of Compound (V) to

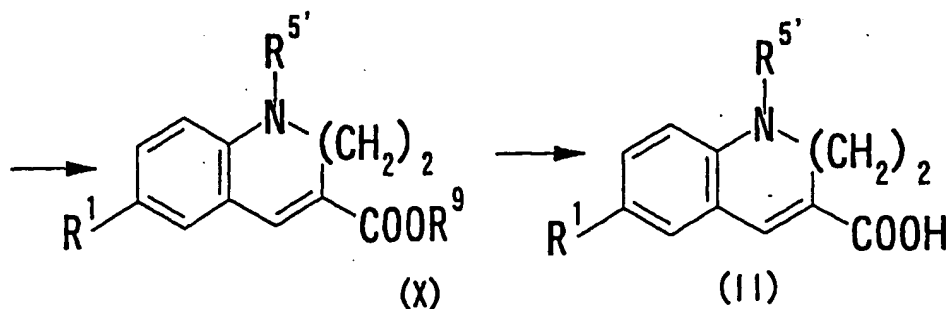
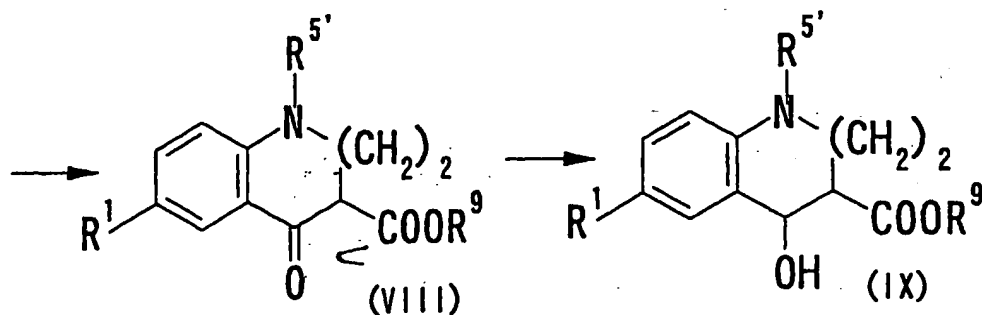
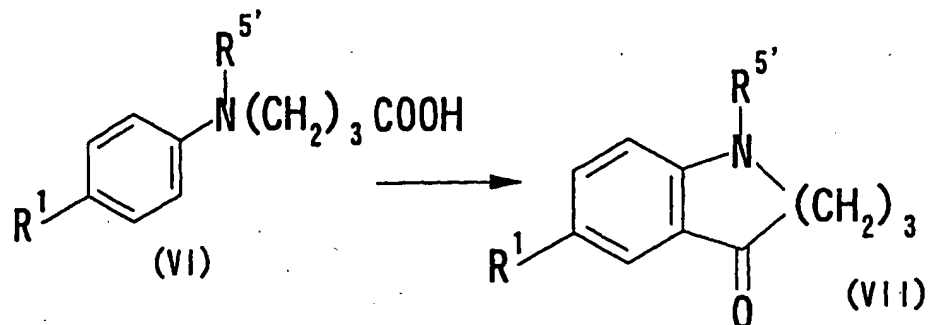
obtain Compound (I).

The thus obtained Compound (I) can be isolated and purified by known separation and purification methods such as concentration, concentration under reduced pressure, extraction, crystallization, recrystallization, solvent convert, chromatography, etc.

Compound (II) used as a starting material can be produced by a known method (e.g. method described in JP-A-73476/1996, etc.) or the methods analogous thereto. For example, Compound (II) can be produced by a method described in the following Reaction Scheme I or II, a method described in the following Reference Examples or the methods analogous thereto.

Reaction Scheme I

10018321.121201



wherein R<sup>9</sup> is a C<sub>1-4</sub> alkyl group, R<sup>5</sup> has the same meaning as the substituent represented by R<sup>5</sup>, and the other symbols are as defined above.

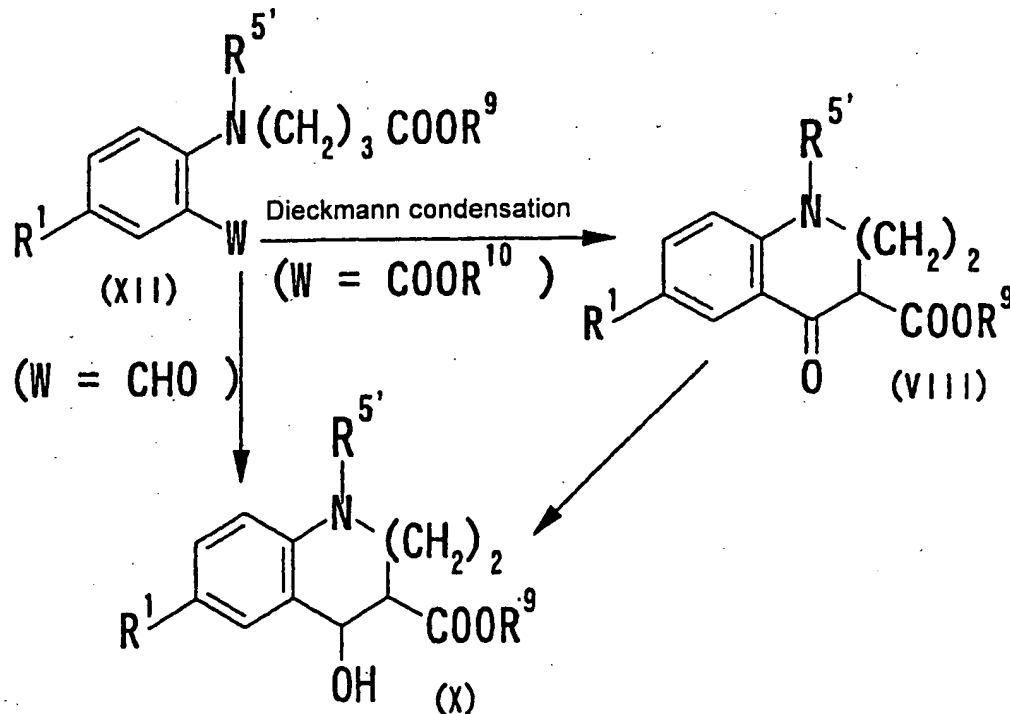
- 5 In this reaction, the Compound (VI) is heated with polyphosphoric acid, or Compound (VI) is converted to acid chloride with thionyl chloride, oxalyl chloride, phosphorus oxychloride, phosphorus pentachloride, etc., followed by subjecting the resulting acid chloride to

usual Friedel-Crafts reaction and cyclizing the same to produce Compound (VII). Compound (VII) is then reacted with carbonate ester in the presence of a base to produce ketoester (VIII). Compound (VIII) is subjected to

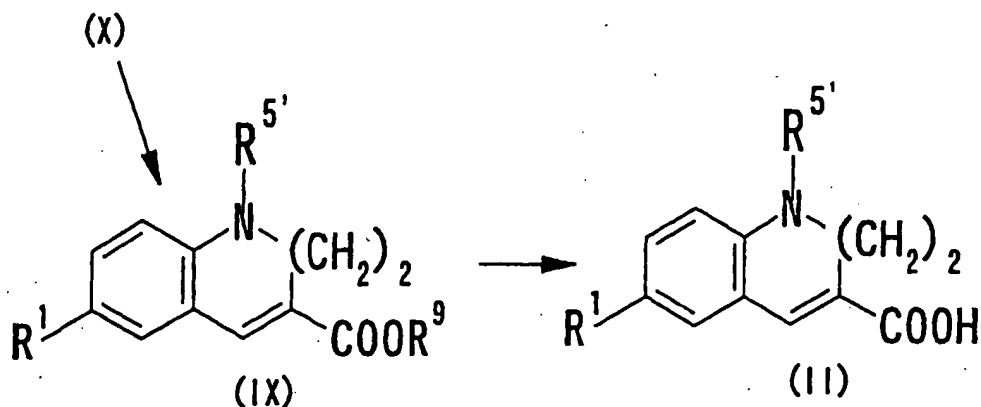
5 reduction with catalytic hydrogenation or sodium borohydride, etc. to produce Compound (IX). Compound (IX) is subjected to dehydration by the conventional method to produce Compound (X). Compound (X) is

10 subjected to ester hydrolysis to produce unsaturated carboxylic acid (II).

## Reaction Scheme II





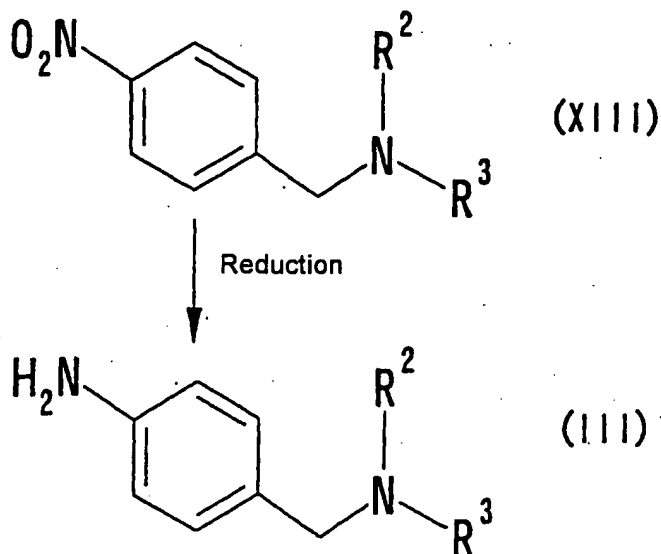


wherein R<sup>10</sup> is C<sub>1-4</sub> alkyl group and the other symbols are as defined above.

The Compound (VIII) or (IX) can be produced by  
 5    subjecting the Compound (XII) to Dieckmann condensation  
 (J. P. Schaefer and J. J. Bloomfield, Org. Reactions,  
 1967, 15, 1). Compound (VIII) or (IX) is subjected to  
 the reactions as described in Reaction Scheme I to  
 produce unsaturated carboxylic acid (II).

10    Compound (III) can be produced by a known method  
 (e.g. method described in JP-A-73476/1996, etc.) or the  
 methods analogous thereto. For example, Compound (III)  
 can be produced by a method described in the following  
 Reaction Scheme III, a method described in the following  
 15    Reference Examples or the methods analogous thereto.

Reaction Scheme 111



The reduction of Compound (XIII) can be carried out by per se known methods, for example, reduction with metal, reduction with metal hydride, reduction with metal hydride complex compound, reduction with metal hydride complex compound, reduction with diborane or substituted borane, catalytic hydrogenation, etc. That is, this reaction is carried out by treating Compound (XIII) with a reducing agent. Examples of the reducing agent include metal such as reduced iron, zinc powder, etc.; alkali metal borohydride (e.g., sodium borohydride, lithium borohydride, etc.); metal hydride complex compound such as aluminum lithium hydride, etc.; metal hydride such as sodium hydride etc.; organic tin compound (triphenyltin hydride, etc.), metal complex compound and metal salt such as nickel compound, zinc compound etc.; catalytic

reducing agent using hydrogen and transition metal catalyst such as palladium, platinum, rhodium, etc.; diborane; etc. Among others, as the reducing agent, catalytic reducing agent using hydrogen and transition metal catalyst such as palladium, platinum, rhodium, etc.; metal such as reduced iron, etc. are preferable. The reaction is carried out in a solvent which does not affect the reaction. Examples of the solvent include benzene, toluene, xylene, chloroform, carbon tetrachloride, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, diethyl ether, tetrahydrofuran, dioxane, methanol, ethanol, propanol, isopropanol, 2-methoxyethanol, N,N-dimethylformamide, acetic acid, or a mixture of these solvents, etc. The solvent is appropriately selected depending on kind of the reducing agent. The reaction temperature is generally about  $-20^{\circ}\text{C}$  to about  $150^{\circ}\text{C}$ , preferably about  $0^{\circ}\text{C}$  to about  $100^{\circ}\text{C}$ , and the reaction time is generally about 1 to about 24 hours.

Amem.  
B20

The thus resulted Compound (II) or (III) can be separated and purified with know separation and purification methods such as concentration, concentration under reduced pressure, extraction, crystallization, solvent conversion, chromatography, etc.

The compound of the formula (I) or a salt thereof of the present invention may be used in combination with

other drug for the treatment or prevention of infectious diseases of HIV (in particular, a pharmaceutical composition for the treatment or prevention of AIDS). In this case, these drugs can be formulated by mixing

5 individually or simultaneously with pharmaceutically acceptable carriers, excipients, binders, diluents or the like, which can be administered orally or non-orally as a pharmaceutical composition for the treatment or prevention of infectious diseases of HIV. In the case of

10 formulating these effective components individually, while the individually formulated agents can be administered in the form of their mixture prepared by using e.g. a diluent when administered, the individually formulated agents can also be administered separately or

15 simultaneously or with time intervals to the one and same subject. A kit for administering the individually formulated effective components in the form of their mixture prepared by using e.g., a diluent when administered (e.g., a kit for injection which comprises

20 two or more ampoules each comprising a powdery component and a diluent for mixing and dissolving two or more components when administered, etc.), a kit for administering the individually formulated agents simultaneously or with time intervals to the one and the

25 same subject (e.g., a kit for tablets to be administered

simultaneously or with time intervals, characterized by having two or more tablets each comprising an agent and said tablets being put in one or separate bags and, if necessary, a column to describe time to be administered each agent, etc.), etc. are also included by the pharmaceutical composition of the present invention.

Example of the other pharmaceutical agent for the treatment or prevention of infectious disease of HIV to be used in combination with the compound of the formula (I) or a salt thereof of the present invention include nucleotide reverse transcriptase inhibitors such as zidovudine, didanosine, zalcitabine, lamivudine, stavudine, abacavir, adefovir, adefovir dipivoxil, fozivudine tidoxil, etc.; non-nucleotide reverse transcriptase inhibitors (including an agent having anti-oxidation activity such as immunocal, oltipraz, etc.) such as nevirapine, delavirdine, efavirenz, loviride, immunocal, oltipraz, etc.; protease inhibitors such as saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, palinavir, lasinavir, etc.; etc.

As the nucleotide reverse transcriptase inhibitor, zidovudine, didanosine, zalcitabine, lamivudine, stavudine, etc. are preferable; as the non-nucleotide reverse transcriptase inhibitor, nevirapine, delavirdine etc. are preferable; and as the protease inhibitor,

saquinavir, ritonavir, indinavir, nelfinavir etc. are preferable.

The compound of the formula (I) or a salt thereof of the present invention may be used in combination with, for example, CXCR4 antagonist (CXCR4 being a second  
5 receptor of T cell-tropic HIV-1) such as AMD-3100, etc., antibody against HIV-1 surface antigen. HIV-1 vaccine, etc., in addition to the above-mentioned protease inhibitor, nucleotide reverse transcriptase inhibitor,  
10 etc.

The compound of the formula (I) or a salt thereof of the present invention has CC chemokine receptor (CCR) antagonistic activity, in particular, potent CCR5  
antagonistic activity and, therefore, can be used for the  
15 treatment or prevention of various infectious diseases of HIV, for example, AIDS in human. The compound of the formula (I) or a salt thereof of the present invention is low toxic and safely used.

The compound of the formula (I) or a salt thereof of the present invention can be used as CCR5 antagonist for  
20 the treatment or prevention of AIDS and also for the prevention of the progression of the AIDS.

The dose per day of the compound of the formula (I) or a salt thereof varies depending on the condition and  
25 body weight of a patient, administration route, etc.

100183221-121201

Typical daily dose per adult patient (body weight: 50Kg) for oral administration is about 5-1000mg, preferably about 10-600mg, more preferably about 10-300mg, and in particular about 15-150mg, as active ingredient [the  
5 compound of the formula (I) or a salt thereof] and the compound of the formula (I) or a salt thereof is administered once or 2-3 times per day.

*Amor.*  
*B2*

10 When the compound of the formula (I) or a salt thereof is used in combination with a reverse transcriptase inhibitor and/or a protease inhibitor. The dose of the reverse transcriptase inhibitor or the protease inhibitor ranges, for example, from about 1/200-1/2 or more of usual dose to about 2-3 times or less of usual dose. In case that two or more drugs are used in  
15 combination, each dose of the drugs is appropriately adjusted if one drug affects metabolism of the other drug, while each dose of the drugs when they are used in combination is generally the same as the dose when they are used alone.

20 Usual doses of the typical reverse transcriptase inhibitors and the protease inhibitors are as follows:

zidovudine : 100mg  
didanosine : 125-200mg  
zalcitabine : 0.75mg  
25 lamivudine : 150mg

- stavudine : 30-40mg  
saquinavir : 600mg  
ritonavir : 600mg  
indinavir : 800mg  
5 nelfinavir : 750mg

In case of combination use of the compound of the formula (I) or a salt thereof with a reverse transcriptase inhibitor and/or a protease inhibitor, preferred embodiments are shown below.

- 10 (1) A drug containing about 10-300mg of the compound of the formula (I) or a salt thereof and a drug containing about 50-200mg of zidovudine to one adult patient (body weight: 50Kg) are administered. Each of the drugs may be administered to the one and the same subject  
15 simultaneously or with time intervals of 12 hours or less.  
(2) A drug containing about 10-300mg of the compound of the formula (I) or a salt thereof and a drug containing about 300-1200mg of saquinavir to one adult patient (body weight: 50Kg) are administered. Each of the drugs may be  
20 administered to the one and the same subject simultaneously or with time intervals of 12 hours or less.

#### Best Mode for Carrying out the Invention

- The present invention is hereinafter described in  
25 more detail by means of the following Test Example.

10018321.121201



Formulation Example, Reference Examples and Working Examples, which are mere examples of the present invention and are not construed as limitative to the present invention.

- 5       The following gene manipulation is carried out in accordance with methods described in textbook (Maniatis et al., Molecular Cloning, Cold Spring Harbor Laboratory, 1989) or protocol attached to reagents.

10       Examples

Test Example

(1) Cloning of human CCR5 chemokine receptor

- 15       Cloning of CCR5 gene was carried out by a PCR method from human spleen cDNA. With using 0.5ng of spleen cDNA (Toyobo, QUICK-Clone cDNA) as template, PCR was performed in DNA Thermal Cycler 480 (Perkin-Elmer) (reaction conditions: 30 cycles of 95°C for 1 minute, 60°C for 1 minute, and 75°C for 5 minutes) by adding each 25 pmol of primers of a primer set,

- 20       SEQ ID NO.: 1 described in Test Example (1) of WO 99/32100 [length of sequence: 34; type of sequence: nucleic acid; strandedness: single; topology: straight; kind of sequence: other nucleic acid synthetic DNA, and  
25       SEQ ID NO.: 2 described in Test Example (1) of WO 99/32100 [length of sequence: 34; type of sequence:

10018331-121201

nucleic acid; strandedness: single; topology: straight;  
kind of sequence: other nucleic acid synthetic DNA  
which were designed referring to nucleotide sequence of  
CCR5 gene reported by Samson et. al. (Biochemistry,

5 35(11), 3362-3367 (1996)) and by using TaKaRa EX Taq  
(Takara Shuzo). The resultant PCR product was subjected  
to agarose gel electrophoresis to collect about 1.0kb DNA  
fragment, which was subjected to Original TA Cloning Kit  
(Funakoshi) to carry out cloning of CCR5 gene.

10 (2) Preparation of plasmid for expression of human CCR5

The plasmid obtained in the above (1) was digested  
with restriction enzymes XbaI (Takara Shuzo) and BamHI  
(Takara Shuzo) and subjected to agarose gel  
electrophoresis to collect about 1.0kb DNA fragment.

15 The DNA fragment was mixed with plasmid pcDNA3.1  
(Funakoshi) for expression in animal cells, said plasmid  
being digested with XbaI and BarnHI, and they were  
ligated with DNA Ligation Kit Ver.2 (Takara Shuzo). The  
resulting plasmid was subjected to transformation of  
20 competent cell of E. coli JM109 (Takara Shuzo) to obtain  
plasmid pCKR5.

(3) Introduction of plasmid for expression of human  
CCR5 into CHO-K1 cell and Expression of said plasmid in  
CHO-K1 cell

25 CHO-K1 cells were grown in 750ml of tissue culture

100183221.121201

*Amen.*  
*B22*

flask (Becton Dickinson) using Ham's F12 medium (Nihon Pharmaceutical) containing 10% fetal calf serum (Life Tech Oriental) and took off with 0.5g/L trypsin-0.2g/L EDTA (Life Tech Oriental). The cells were washed with PBS (Life Tech Oriental), centrifuged (1000rpm, 5 minutes), and suspended in PBS. With using Gene Pulser (Bio-Rad Laboratories), DNA was introduced into the cells under the conditions shown below. That is, to the cuvette of 0.4cm gap were added  $8 \times 10^6$  cells and 10 $\mu$ g of plasmid pCKR5 for expression of human CCR5, and electroporation was carried out under 0.25kV of voltage and 960 $\mu$ F of capacitance. The cells were transferred into Ham's F12 medium containing 10% fetal calf serum, and cultivated for 24 hours. The cells were again took off and centrifuged, and suspended in Ham's F12 medium containing 10% fetal calf serum and 500 $\mu$ g/ml of geneticin (Life Tech Oriental). The suspension was diluted to give 104 cells/ml of the suspension, which was inoculated on 96 well plate (Becton Dickinson) to give geneticin resistant cells.

The resulting geneticin resistant cells were cultivated in 96 well plate (Becton Dickinson), and cells expressing CCR5 were selected from the geneticin resistant cells. That is, in assay buffer (Ham's F12 medium containing 0.5% BSA and 20mM HEPES (Wako Pure

Chemical, pH7.2)) to which was added 200pM of [<sup>125</sup>I]-  
RANTES (Amersham) as a ligand, a binding reaction was  
carried out at room temperature for 40 minutes, and the  
buffer was washed with cooled PBS. To the buffer was  
5 added 50μl/well of 1M NaOH, and the mixture was stirred.  
Radioactivity was determined with a γ-counter to select  
CCR5/CHO cells which specifically bind to the ligand.

(4) Evaluation of Test Compounds based on CCR5  
antagonistic activity

10 The CCR5/CHO cells were inoculated on 96 well  
microplate (5 × 10<sup>4</sup> cells/well) and cultivated for 24  
hours. The medium was removed by means of suction, and  
to each well was added an assay buffer containing Test  
Compound (1μM) and then 100pM of [<sup>125</sup>I]-RANTES (Amersham)  
15 as a ligand. A binding assay was carried out at room  
temperature for 40 minutes, and an assay buffer was  
removed by means of suction. Each well was washed twice  
with cooled PBS, and 200μl of Microscint-20 (Packard  
Instrument, Inc.) was added to each well. Radio-activity  
20 was determined with Top-Count Micro Scintillation Counter  
(Packard Instrument, Inc.).

According to the method described above, inhibitory  
rate of Test Compound to CCR5 binding was measured. The  
results are shown in Table 1.

Table 1

| Compound Number | Inhibitory Rate (%) |
|-----------------|---------------------|
| 1               | 93                  |
| 2               | 96                  |
| 14              | 96                  |
| 16              | 96                  |
| 17              | 99                  |
| 19              | 100                 |
| 20              | 94                  |
| 23              | 97                  |
| 26              | 100                 |
| 27              | 100                 |
| 33              | 98                  |
| 35              | 100                 |
| 39              | 98                  |
| 43              | 100                 |
| 45              | 100                 |
| 49              | 100                 |
| 50              | 100                 |
| 58              | 99                  |
| 68              | 95                  |
| 69              | 100                 |
| 71              | 100                 |
| 77              | 97                  |
| 79              | 100                 |
| 84              | 97                  |
| 85              | 100                 |
| 98              | 100                 |
| 101             | 100                 |
| 102             | 100                 |
| 104             | 98                  |
| 112             | 100                 |

10018321-121201

(5) Inhibitory effect on HIV-1 infection to MAGI-CCR5 cell

The plasmid where  $\beta$ -galactosidase gene was ligated downstream of HIV-1 LTR was introduced into CD4 positive HeLa cell, to which human CCR5 was further introduced to obtain transformant MAGI-CCR5.

By using said transformant MAGI-CCR5, a degree of HIV-1 infection was calculated using  $\beta$ -galactosidase activity (blue color due to decomposition of 5-bromo-4-chloro-3-indolyl- $\beta$ -D-galactopyranoside) as an index. Specifically, MAGI-CCR5 cells were suspended in DMEM medium containing 10% serum to prepare  $5 \times 10^4$  cells/ml suspension. To each well of 96 well plate was inoculated 200 $\mu$ l of the suspension, and the cells were cultivated at 37°C overnight. The medium was removed by means of suction, and to the residue was added 100 $\mu$ l of the above medium containing 1.6 $\mu$ M of Test Compound and 100 $\mu$ l of the above medium containing 300PFU of HIV-1 BA-L cells. The cells were cultivated at 37°C for 2 days. The medium was removed by means of suction. To the residue was added 200 $\mu$ l of a cell fixative (PBS containing 1% formaldehyde and 0.2% glutaraldehyde), and the mixture was allowed to stand at room temperature for 5 minutes and washed twice with PBS. To the mixture was added 100 $\mu$ l of staining solution (PBS containing 4 $\mu$ M potassium ferrocyanide, 4 $\mu$ M

Amem  
B23

potassium ferricyanade, 2 $\mu$ M MgCl<sub>2</sub>, and 0.4mg/ml X-gal), and the mixture was allowed to stand at 37°C for 50 minutes and washed twice with PBS. The number of blue cells was counted by a microscope and defined as the number of cells infected with HIV-1. According to this method, inhibition rate on HIV-1 infection was determined. The results are shown in Table 2.

Table 2

| Compound Number | Inhibition Rate (%) |
|-----------------|---------------------|
| 1               | 85                  |
| 14              | 91                  |
| 16              | 94                  |
| 17              | 94                  |

The pharmaceutical composition for antagonizing CCR5 (e.g., a medicament for the treatment or prevention of infectious disease of HIV, a medicament for the treatment or prevention of AIDS, etc.) comprising the compound of the formula (I) or a salt thereof of the present invention, as an active ingredient, can be prepared, for example, by the following prescriptions:

## Formulation Example

## 1. Capsule

- (1) Compound obtained in Working Example 1 40mg  
(2) lactose 70mg

(3) fine crystalline cellulose 9mg

(4) magnesium stearate 1mg

1 capsule 120mg

(1), (2), (3) and 1/2 of (4) are mixed and then  
5 granulated. To the granules is added the remainder of  
(4), and the whole is filled into a gelatin capsule.

## 2. Tablet

(1) Compound obtained in Working Example 1 40mg

(2) lactose 58mg

10 (3) corn starch 18mg

(4) fine crystalline cellulose 3.5mg

(5) magnesium stearate 0.5mg

1 capsule 120mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed  
15 and then granulated. To the granules are added the  
remainders of (4) and (5), followed by subjecting the  
mixture to compression molding.

## Reference Example 1

In DMF (14ml) was dissolved 1- formyl-7-(4-  
20 morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-  
carboxylic acid (0.18g). To the solution was added,  
under ice-cooling, thionyl chloride (0.1ml), and the  
mixture was stirred at room temperature for 30 minutes.  
Under reduced pressure, the solvent was evaporated, and  
25 the residue was suspended in THF (50ml). The suspension

100183221.121201



was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.13g) and triethylamine (0.33ml) in THF (5ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethanol/hexane to give 1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.16g) as colorless crystals.

mp 234 - 243°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.70 - 1.75 (4H, m), 2.21 (3H, s), 2.60 - 2.67 (1H, m), 3.03 (2H, t, J = 5.4 Hz), 3.21 - 3.26 (4H, m), 3.37 (2H, dt, J = 2.8, 11.2 Hz), 3.58 (2H, s), 3.87 - 3.95 (6H, m), 4.02 - 4.07 (2H, m), 7.00 (2H, d, J = 8.8 Hz), 7.19 (1H, d, J = 8.6 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.47 - 7.59 (7H, m), 7.69 (1H, d, J = 2.2 Hz), 8.55 (1H, s).

IR (KBr) v: 2953, 2845, 1667 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>35</sub>H<sub>40</sub>N<sub>4</sub>O<sub>4</sub>: C, 72.39; H, 6.94; N, 9.65.

Found C, 72.03; H, 6.65; N, 9.49.

## Reference Example 2

In DMF (5ml) was dissolved 7-(4-ethoxyphenyl)-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.2g). To the solution was added, under ice-cooling, thionyl chloride (0.11ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and the residue was suspended in THF (15ml). The suspension was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.15g) and triethylamine (0.41ml) in THF (5ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 7-(4-ethoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.25g) as colorless crystals. mp 211 - 215°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.45 (3H, t, J = 6.9 Hz), 1.59 - 1.75 (4H, m), 2.21 (3H, s), 2.60 - 2.68 (1H, m), 3.04 (2H, t, J

= 5.5 Hz), 3.37 (2H, dt, J = 2.8, 11.3 Hz), 3.58 (2H, s),  
3.93 (2H, t, J = 5.5 Hz), 4.01 - 4.18 (4H, m), 6.99 (2H, d,  
J = 8.8 Hz), 7.19 (1H, d, J = 8.6 Hz), 7.32 (2H, d, J = 8.4  
Hz), 7.46 - 7.58 (6H, m), 7.68 (1H, d, J = 2.0 Hz), 8.55  
5 (1H, s).

IR (KBr)  $\nu$ : 2940, 1667  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{33}\text{H}_{37}\text{N}_3\text{O}_4 \cdot 0.2\text{H}_2\text{O}$ : C, 72.96; H, 6.94; N, 7.73.  
Found C, 72.89; H, 6.91; N, 7.59.

#### Reference Example 3

10 In DMF (5ml) was dissolved 7-(3-diethoxyphenyl)-1-  
formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid  
(0.25g). To the solution was added, under ice-cooling,  
thionyl chloride (0.12ml), and the mixture was stirred at  
room temperature for 30 minutes. Under reduced pressure,  
15 the solvent was evaporated, and the residue was suspended  
in THF (25ml). The solution was added dropwise to a  
solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-  
yl)aminomethyl]aniline (0.16g) and triethylamine (0.46ml)  
in THF (4ml), under ice-cooling, and the mixture was  
20 stirred under nitrogen atmosphere at room temperature for  
5 hours. Under reduced pressure, the solvent was  
evaporated. To the residue was added water, and the  
mixture was extracted with ethyl acetate. The organic  
layer was washed with water and saturated brine and dried  
25 with anhydrous magnesium sulfate, and the solvent was

evaporated to give crude crystals, which were recrystallized from ethyl acetate/diethyl ether to give 7-(3,4-diethoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.26g) as yellow crystals.

mp 145 - 148°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.49 (3H, t, J = 7.0 Hz), 1.50 (3H, t, J = 7.0 Hz), 1.62 - 1.75 (4H, m), 2.21 (3H, s), 2.61 - 2.70 (1H, m), 3.04 (2H, t, J = 5.4 Hz), 3.38 (2H, dt, J = 3.0, 11.2 Hz), 3.58 (2H, s), 3.93 (2H, t, J = 5.4 Hz), 3.95 - 4.10 (2H, m), 4.10 - 4.24 (4H, m), 6.97 (1H, d, J = 8.8 Hz), 7.11 - 7.21 (3H, m), 7.33 (2H, d, J = 8.4 Hz), 7.49 - 7.59 (4H, m), 7.68 (1H, d, J = 2.0 Hz), 8.55 (1H, s).

IR (KBr) v: 2980, 2944, 1667 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>33</sub>H<sub>41</sub>N<sub>3</sub>O<sub>5</sub>·0.2H<sub>2</sub>O: C, 71.58; H, 7.10; N, 7.15. Found C, 71.40; H, 7.00; N, 7.22.

#### Reference Example 4

In DMF (10ml) was dissolved 1-methanesulfonyl-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.3g). To the solution was added, under ice-cooling, thionyl chloride (0.15ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and the residue was suspended in THF (50ml). The suspension was

added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.19g) and triethylamine (0.5ml) in THF (5ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/ethanol to give 1-methanesulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.26g) as pale crystals.

mp 239 - 243°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.70 - 1.77 (4H, m), 2.22 (3H, s), 2.60 - 2.70 (1H, m), 2.89 (3H, s), 3.13 (2H, t-like), 3.21 - 3.26 (4H, m), 3.37 (2H, dt, J = 2.6, 11.5 Hz), 3.59 (2H, s), 3.87 - 3.91 (6H, m), 4.02 - 4.11 (2H, m), 7.00 (2H, d, J = 8.8 Hz), 7.34 (2H, d, J = 8.8 Hz), 7.50 - 7.66 (9H, m).

IR (KBr) v: 2951, 2847, 1661, 1609, 1520 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>35</sub>H<sub>42</sub>N<sub>4</sub>O<sub>5</sub>S·0.3H<sub>2</sub>O: C, 66.08; H, 6.75; N, 8.81. Found C, 66.06; H, 6.50; N, 8.55.

Amen.  
B24

10018321.121201

In DMF (12ml) was suspended 7-(4-ethoxyphenyl)-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.13g). To the suspension was added, under ice-cooling, thionyl chloride (0.04ml) and DMF (catalytic amount), and the mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (15ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.08g) and triethylamine (0.14ml) in THF (5ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 7-(4-ethoxyphenyl)-1-methanesulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.16g) as colorless crystals.

mp 184 - 186°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.45 (3H, t, J = 7.0 Hz), 1.64 - 1.75 (4H, m), 2.21 (3H, s), 2.61 - 2.72 (1H, m), 2.88 (3H, s),

3.13 (2H, t,  $J = 5.3$  Hz), 3.37 (2H, dt,  $J = 2.6, 11.2$  Hz),  
3.59 (2H, s), 3.91 (2H, t,  $J = 5.3$  Hz), 4.01 - 4.07 (2H, m),  
4.09 (2H, q,  $J = 7.0$  Hz), 6.98 (2H, d,  $J = 8.8$  Hz), 7.33  
(2H, d,  $J = 8.8$  Hz), 7.48 - 7.68 (9H, m).

5 IR (KBr)  $\nu$ : 2946, 2843, 1661, 1609, 1518, 1495  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{33}\text{H}_{39}\text{N}_3\text{O}_5\text{S}$ : C, 67.21; H, 6.67; N, 7.13.

Found C, 67.25; H, 6.33; N, 7.05.

#### Reference Example 6

10 In DMF (8ml) was dissolved 1-methoxycarbonyl-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.15g). To the solution was added, under ice-cooling, thionyl chloride (0.07ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and  
15 the residue was suspended in THF (25ml). The suspension was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.12g) and triethylamine (0.26ml) in THF (5ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at  
20 room temperature for 4 hours. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the  
25 solvent was evaporated. The residue was purified with

silica gel column chromatography (elution solvent: methanol/triethylamine/ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 1-methoxycarbonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.14g) as colorless crystals.

mp 193 - 197°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.57 - 1.80 (4H, m), 2.21 (3H, s), 2.65 (1H, br), 3.03 (2H, br), 3.20 - 3.23 (4H, m), 3.37 (2H, dt, J = 3.0, 9.9 Hz), 3.58 (2H, s), 3.78 (3H, s), 3.78 (2H, br), 3.87 - 3.92 (4H, m), 4.01 - 4.14 (2H, m), 6.99 (2H, d, J = 9.2 Hz), 7.30 - 7.60 (10H, m).

IR (KBr) v: 2957, 2855, 1701 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>36</sub>H<sub>42</sub>N<sub>4</sub>O<sub>5</sub>·0.2H<sub>2</sub>O: C, 70.38; H, 6.96; N, 9.12. Found C, 70.35; H, 6.81; N, 9.09.

#### Reference Example 7

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved 3,4-diethylphenyl borate (264mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (406mg), and to the solution was added potassium carbonate (162mg). The mixture was stirred under argon atmosphere at room temperature for 30 minutes, and to the mixture was added



tetrakis(triphenylphosphine)palladium (39mg). The mixture was refluxed under argon atmosphere for 13 hours, diluted with ethyl acetate and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (45g, ethyl acetate : ethanol = 20 : 1) and recrystallized from ethanol to give 7-(3,4-diethylphenyl)-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (263mg, 55%) as yellow crystals.

mp 127 - 129°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.47 (3H, t, J = 7.0 Hz), 1.48 (3H, t, J = 7.0 Hz), 1.69 - 1.76 (4H, m), 2.21 (3H, s), 2.53 - 2.74 (1H, m), 2.96 (2H, t, J = 4.5 Hz), 3.09 (3H, s), 3.31 - 3.43 (4H, m), 3.57 (2H, s), 4.01 - 4.07 (2H, m), 4.13 (2H, q, J = 7.0 Hz), 4.17 (2H, q, J = 7.0 Hz), 6.87 (1H, d, J = 8.6 Hz), 6.93 (1H, d, J = 9.0 Hz), 7.07 (1H, dd, J = 6.9, 2.1 Hz), 7.09 (1H, s), 7.30 (2H, d, J = 8.6 Hz), 7.41 - 7.42 (2H, m), 7.48 (1H, dd, J = 9.1, 2.3 Hz), 7.54 (2H, d, J = 8.6 Hz), 7.59 (1H, s).

IR (KBr) 1653, 1599, 1514, 1503, 1478, 1406, 1312, 1246, 1188, 1140, 1044 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>35</sub>H<sub>43</sub>N<sub>3</sub>O<sub>4</sub>: C, 73.78; H, 7.61; N, 7.38.

Found C, 73.49; H, 7.54; N, 7.15.

#### Reference Example 8

100183321.121201  
In a mixture of THF and ethanol (1 : 1, v/v, 30.0ml) was dissolved ethyl 1-[(4-methylphenyl)sulfonyl]-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (454mg). To the solution was added 1N sodium hydroxide solution (3.0ml), and the mixture was stirred at room temperature for 62 hours. To the mixture was added 1N hydrochloric acid to make the solution weak acidic, and the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 1-[(4-methylphenyl)sulfonyl]-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid as white crystals. The obtained 1-[(4-methylphenyl)sulfonyl]-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid was suspended in DMF(15.0ml). To the suspension was added thionyl chloride (0.15ml), and the mixture was stirred at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in dichloromethane (10.0ml). On the other hand, to 4-[(N-methyl-N-tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (296mg) was added dichloromethane (15.0ml), and then was added triethylamine (0.88ml). To

the obtained mixture was added dropwise at 0°C the previously prepared acid chloride solution, and the mixture was stirred at room temperature for 3 hours. To the mixture was added water, and the separated organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was recrystallized from ethanol to give 1-[(4-methylphenyl)sulfonyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (359mg, 60%) as white crystals.

mp 258 - 262°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.70 - 1.77 (4H, m), 2.21 (3H, s), 2.35 (3H, s), 2.53 - 2.74 (1H, m), 2.98 (2H, t, J = 5.5 Hz), 3.23 (4H, t, J = 4.9 Hz), 3.38 (2H, td, J = 10.4, 3.2 Hz), 3.58 (2H, s), 3.89 (4H, t, J = 4.8 Hz), 3.99 (2H, t, J = 5.4 Hz), 4.01 - 4.09 (2H, m), 6.99 (2H, d, J = 8.8 Hz), 6.97 - 7.06 (2H, m), 7.19 (2H, d, J = 7.6 Hz), 7.29 - 7.34 (2H, m), 7.45 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.6 Hz), 7.50 - 7.65 (5H, m).

IR (KBr) 1663, 1609, 1605, 1518, 1495, 1345, 1308, 1233, 1159, 1121, 1090, 928, 816, 733, 671 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>41</sub>H<sub>46</sub>N<sub>4</sub>O<sub>5</sub>S (0.1H<sub>2</sub>O additive): C, 69.49; H, 6.57; N, 7.91. Found C, 69.27; H, 6.63; N, 7.92.

Reference Example 9

In DMF (15.0ml) was suspended 1-acetyl-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (365mg). To the suspension was added thionyl chloride (0.17ml), and the mixture was stirred at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in dichloromethane (10.0ml). On the other hand, to 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (327mg) was added dichloromethane (15.0ml), and then was added triethylamine (0.97ml). To the obtained mixture: was added dropwise the previously prepared acid chloride suspension at 0°C, and the mixture was stirred at room temperature for 3 hours. To the mixture was added water, and the separated organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (50g, ethyl acetate : ethanol = 9 : 1) and washed with hexane/ethyl acetate to give 1-acetyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (116mg, 21%) as pale yellow crystals.

mp 141 - 145°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.65 - 1.87 (4H, m), 2.09 (3H, s), 2.23 (3H, s), 2.61 - 2.78 (1H, m), 2.81 - 3.05 (3H, m),

3.24 (4H, t,  $J = 4.7$  Hz), 3.37 (2H, td,  $J = 11.4, 2.7$  Hz),  
3.60 (2H, s), 3.90 (4H, t,  $J = 4.8$  Hz); 4.02 - 4.07 (2H, m),  
4.75 - 4.91 (1H, m), 7.23 - 7.27 (1H, m), 7.34 (2H, d,  $J =$   
8.4 Hz), 7.52 - 7.69 (8H, m).

5 IR (KBr) 1657, 1609, 1514, 1497, 1451, 1395, 1314, 1258,  
1235  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{36}\text{H}_{42}\text{N}_4\text{O}_4$  (1.2 $\text{H}_2\text{O}$  additive): C, 70.15; H,  
7.26; N, 9.09. Found C, 69.91; H, 7.05; N, 9.03.

#### Reference Example 10

10 In water : ethanol : toluene (1 : 1 : 10, v/v,  
18.0ml) were dissolved (4-diethylamino)phenyl borate  
(234mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-  
(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-  
dihydro-1H-1-benzazepine-4-carboxamide (391mg). To the  
15 solution was added potassium carbonate (268mg), and the  
mixture was stirred under argon atmosphere at room  
temperature for 30 minutes. To the mixture was added  
tetrakis(triphenylphosphine)palladium (37mg), and the  
mixture was heated to reflux under argon atmosphere for  
20 10 hours. The mixture was diluted with ethyl acetate,  
and washed with water and saturated brine, and the  
organic layer was dried with anhydrous magnesium sulfate.  
The solvent was evaporated under reduced pressure, and  
the residue was purified with silica gel column  
25 chromatography (45g, ethyl acetate:ethanol=20:1) and

recrystallized from ethanol to give 7-(4-diethylaminophenyl)-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (145mg, 33%) as  
 5 yellow crystals.

mp 178 - 180°C.

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 1.19 (6H, t, J = 7.0 Hz), 1.64 - 1.76 (4H, m), 2.21 (3H, s), 2.54 - 2.72 (1H, m), 2.95 (2H, t, J = 4.5 Hz), 3.07 (3H, s), 3.31 - 3.44 (4H, m), 3.39 (4H, q, J = 7.1 Hz), 3.57 (2H, s), 4.01 - 4.07 (2H, m), 6.74 (2H, d, J = 9.0 Hz), 6.86 (1H, d, J = 8.6 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.41 - 7.59 (8H, m).  
 10

IR (KBr) 2948, 1644, 1597, 1514, 1497, 1406, 1312, 1283, 1246, 1188, 1071, 810, 733 cm<sup>-1</sup>.

15 Anal. Calcd. for C<sub>35</sub>H<sub>44</sub>N<sub>4</sub>O<sub>2</sub> (0.1H<sub>2</sub>O additive): C, 75.80; H, 8.03; N, 10.10. Found C, 75.51; H, 7.95; N, 10.10.

~~Reference Example 11~~

*Amen. B25*  
 In water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved 4-propoxyphenyl borate (203mg) and  
 20 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide(455mg). To the solution was added potassium carbonate (312mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To  
 25 the mixture was added tetrakis(triphenylphosphine)palladium

(43mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (30g, ethyl acetate : ethanol : triethyleamine = 100 : 5 : 1) and recrystallized from ethanol/hexane to give 1-methyl-N-[4-[[ N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxamide (349mg, 69%) as yellow crystals.

mp 149 - 151°C.

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 1.05 (3H, t, J = 7.4 Hz), 1.63 - 1.76 (4H, m), 1.83 (2H, sextet, J = 7.2 Hz), 2.20 (3H, s), 2.53 - 2.73 (1H, m), 2.95 (2H, t, J = 4.5 Hz), 3.07 (3H, s), 3.31 - 3.43 (4H, m), 3.56 (2H, s), 3.96 (2H, t, J = 6.6 Hz), 4.01 - 4.07 (2H, m), 6.87 (1H, d, J = 8.4 Hz), 6.95 (2H, d, J = 8.8 Hz), 7.29 (2H, d, J = 8.6 Hz), 7.39 (1H, s), 7.43 (1H, dd, J = 8.6, 2.2 Hz), 7.47 (2H, d, J = 8.6 Hz), 1H (d) was concealed under 7.49, 7.54 (2H, d, J = 8.6 Hz), 7.62 (1H, s).

IR (KBr) 2946, 1651, 1607, 1514, 1505, 1312, 1242, 1182, 814 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>34</sub>H<sub>41</sub>N<sub>3</sub>O<sub>3</sub> (0.1H<sub>2</sub>O additive): C, 75.41; H,

7.67; N, 7.76. Found C, 75.30; H, 7.75; N, 7.82.

#### Reference Example 12

In DMF (10.0ml) was suspended 1-formyl-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (433mg). To the suspension was added thionyl chloride (0.22ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and to the mixture was added THF (15.0ml). On the other hand, to 4-[[N-methyl-N-tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (434mg) was added THF (10.0ml) and then added triethylamine (1.29ml). The previously prepared acid chloride suspension was added dropwise at 0°C. The mixture was stirred at room temperature for 4 hours. To the mixture was added water, and the mixture was washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was recrystallized from ethanol to give 1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxamide (554mg, 81%) as white crystals.

mp 207 - 209°C.

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 1.06 (3H, t, J = 7.4 Hz), 1.63 - 1.77 (4H, m), 1.85 (2H, sextet, J = 7.0 Hz), 2.21 (3H, s),



2.57 - 2.72 (1H, m), 3.04 (2H, t, J = 4.8 Hz), 3.37 (2H, td, J = 11.4, 3.1 Hz), 3.57 (2H, s), 3.90 - 4.08 (6H, m), 7.00 (2H, d, J = 9.0 Hz), 7.20 (1H, d, J = 8.2 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.47 - 7.54 (6H, m), 7.57 (1H, dd, J = 8.0, 2.2 Hz), 7.68 (1H, d, J = 2.0 Hz), 8.56 (1H, s).

IR (KBr) 1669, 1609, 1522, 1497, 1360, 1314, 1252  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{34}\text{H}_{39}\text{N}_3\text{O}_4$ : C, 73.75; H, 7.10; N, 7.59.

Found C, 73.48; H, 7.11; N, 7.50.

## Reference Example 13

10 In THF (10.0ml) and catalytic amount of DMF was suspended 1-methylsulfonyl-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (236mg). To the suspension was added oxalyl chloride (0.13ml), and the mixture was stirred at room temperature for 1 hour.

15 Under reduced pressure, the solvent was evaporated. To the residue was added THF (10.0ml). On the other hand, to 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (207mg) was added THF (10.0ml), and then was added triethylamine (0.61ml).

20 To the obtained mixture was added dropwise at 0°C the previously prepared acid chloride suspension, and the mixture was stirred at room temperature for 3.5 hours. To the mixture was added ethyl acetate, and the mixture was washed with water, 1N sodium hydroxide solution,

25 water and saturated brine. The organic layer was dried

10018321-121201

with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (10g, ethyl acetate : ethanol : triethylamine = 100 : 10 : 1) and recrystallized from ethanol to give 1-methylsulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxamide (205mg, 58%) as white crystals.

10 mp 199 - 202°C.

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 1.06 (3H, t, J = 7.4 Hz), 1.63 - 1.79 (4H, m), 1.85 (2H, sextet, J = 7.0 Hz), 2.21 (3H, s), 2.54 - 2.74 (1H, m), 2.98 (3H, s), 3.14 (2H, t, J = 5.2 Hz), 3.38 (2H, td, J = 11.3, 3.2 Hz), 3.58 (2H, s), 3.89 - 4.07 (6H, m), 6.96 - 7.03 (2H, m), 7.33 (2H, d, J = 8.4 Hz), 7.47 - 7.67 (9H, m).

15

IR (KBr) 1653, 1609, 1518, 1493, 1341, 1314, 1248, 1154 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>34</sub>H<sub>41</sub>N<sub>3</sub>O<sub>5</sub>S: C, 67.64; H, 6.84; N, 6.96.

20 Found C, 67.37; H, 6.77; N, 6.89.

#### Reference Example 14

In THF (10.0ml) and catalytic amount of DMF was suspended 7-(4-ethoxy-3-fluorophenyl)-1-methylsulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (182mg).

25 To the suspension was added oxalyl chloride (0.12ml), and

the mixture was stirred at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated, and to the residue was added THF (10.0ml). On the other hand, to 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl] aniline dihydrochloride (158mg) was added THF (10.0ml), and then was added triethylamine (0.47ml). To the obtained mixture was added dropwise at 0°C the previously prepared acid chloride suspension, and the mixture was stirred at room temperature for 3 hours. To the mixture was added ethyl acetate, and the mixture was washed with water, N sodium hydroxide solution, water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (15g, ethyl acetate → ethyl acetate : ethanol : triethylamine = 100 : 10 : 1), and recrystallized from ethanol to give 7-(4-ethoxy-3-fluorophenyl)-1-methylsulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (140mg, 51%) as white crystals.

mp 199 - 202°C.

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 1.49 (3H, t, J = 7.0 Hz), 1.64 - 1.77 (4H, m), 2.21 (3H, s), 2.57 - 2.70 (1H, m), 2.89 (3H, s), 3.14 (2H, t, J = 5.4 Hz), 3.38 (2H, td, J = 11.3, 2.9

Amer.  
B26

10018331-121201

Hz), 3.57 (2H, s, 3.91 (2H, t,  $J = 5.7$  Hz), 4.02 - 4.07 (2H, m), 4.17 (2H, q,  $J = 6.9$  Hz), 7.04 (1H, t,  $J = 8.8$  Hz), 7.28 - 7.35 (3H, m), 7.48 - 7.61 (7H, m), 7.65 (1H, d,  $J = 8.4$  Hz).

5 IR (KBr) 1661, 1522, 1497, 1343, 1310, 1269, 1238, 1154, 1138  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{33}\text{H}_{38}\text{FN}_3\text{O}_5\text{S}$  (0.3 $\text{H}_2\text{O}$  additive)] C, 64.64; H, 6.35; N, 6.85. Found C, 64.46; H, 6.41; N, 6.80.

#### Reference Example 15

10 In DMF (5.5ml) was dissolved 7-(4-ethoxy-3-fluorophenyl)-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (398mg). To the solution was added thionyl chloride (0.20ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, 15 the solvent was evaporated, and to the residue was added THF (10.0ml). On the other hand, to 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (394mg) was added THF (10.0ml), and then was added triethylamine (1.17 ml). To the obtained 20 mixture was added dropwise at 0°C the previously prepared acid chloride suspension, and the mixture was stirred at room temperature for 4 hours. To the mixture was added ethyl acetate, and the mixture was washed with water, 1N sodium hydroxide solution, water and saturated brine. 25 The organic layer was dried with anhydrous magnesium

sulfate. The solvent was evaporated under reduced pressure, and the residue was recrystallized from ethanol to give 7-(4-ethoxy-3-fluorophenyl)-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-  
5 2,3-dihydro-1H-1-benzazepine-4-carboxamide (453mg, 73%) as white crystals.

mp 193 - 196°C.

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 1.49 (3H, t, J = 7.0 Hz), 1.64 - 1.75 (4H, m), 2.21 (3H, s), 2.58 - 2.74 (1H, m), 3.04 (2H, t, J = 5.0 Hz), 3.37 (2H, td, J = 11.3, 3.1 Hz), 3.58 (2H, s), 3.92 (2H, t, J = 5.3 Hz), 4.02 - 4.07 (2H, m), 4.17 (2H, q, J = 7.1 Hz), 7.05 (1H, t, J = 8.6 Hz), 7.20 (1H, d, J = 8.4 Hz), 7.29 - 7.37 (5H, m), 7.45 (1H, s), 7.54 (2H, d, J = 8.4 Hz), 7.56 (1H, s), 7.66 (1H, d, J = 2.0 Hz), 8.55 (1H, s).  
15

IR (KBr) 1667, 1514, 1501, 1360, 1314, 1269, 1238 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>33</sub>H<sub>36</sub>FN<sub>3</sub>O<sub>4</sub> (0.1H<sub>2</sub>O additive): C, 70.85; H, 6.52; N, 7.51. Found C, 70.55; H, 6.54; N, 7.45.

#### Reference Example 16

20 A solution of methyl 5-bromo-N-tosylanthranilate (200g) in DMF (450ml) was added dropwise, under ice-cooling, to a suspension of 60% sodium hydride (25g) in DMF (50ml). Under nitrogen atmosphere, the mixture was stirred at room temperature for 2 hours, and to the  
25 mixture were added sodium iodide (78g) and ethyl 4-

Ammon.  
B27

bromobutyrate (82ml). The mixture was stirred under nitrogen atmosphere at 85°C for 24 hours, and to the mixture was added potassium t-butoxide (70g) under ice-cooling. The mixture was stirred at 85°C for 1.5 hours, and the solvent was evaporated. To the residue was added ice-water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give ethyl (methyl) 7-bromo-5-hydroxy-1-tosyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (mixture) (153g) as white crystals.

<sup>1</sup>H NMR (δ ppm, CDCl<sub>3</sub>) 1.31 (1.5H, t, J = 7.1 Hz), 2.29 (2H, t, J = 6.4 Hz), 2.40 (3H, s), 3.72 (1.5H, s), 4.08 (2H, t, J = 6.4 Hz), 4.17 (1H, q, J = 7.1 Hz), 7.17 (2H, d, J = 8.2 Hz), 7.38 (2H, d, J = 8.0 Hz), 7.41 - 7.46 (1H, m), 7.60 - 7.66 (2H, m), 11.83 (0.5H, s), 11.91 (0.5H, s).

#### Reference Example 17

To ethyl (methyl) 7-bromo-5-hydroxy-1-tosyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (mixture) (32.4g) were added acetic acid (200ml) and concentrated sulfuric acid (120ml), and the mixture was stirred at 80°C for 2.5 hours. The mixture was poured into ice-water, and the mixture was neutralized with sodium hydroxide solution and extracted with ethyl acetate. The organic layer was

washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column chromatography (hexane/ethyl acetate) to give 7-bromo-1,2,3,4-tetrahydro-1-benzazepin-5-one (8.55g) as pale yellow crystals.

mp 99 - 101°C.

<sup>1</sup>H NMR ( $\delta$  ppm, CDCl<sub>3</sub>) 2.18 (2H, quint, J = 7.1 Hz), 2.82 (2H, t, J = 7.2 Hz), 3.25 (2H, t, J = 6.6 Hz), 4.65 (1H, br), 6.65 (1H, d, J = 8.6 Hz), 7.20 (1H, dd, J = 2.2, 8.6 Hz), 7.82 (1H, d, J = 2.2 Hz).

IR (KBr)  $\nu$ : 3364, 2955, 1661 cm<sup>-1</sup>.

#### Reference Example 18

In THF (200ml) were dissolved 7-bromo-1,2,3,4-tetrahydro-1-benzazepin-5-one (7g) and dimethylaminopyridine (22g). To the solution was added di-t-butyl dicarbonate (60g), and the mixture was refluxed for 1.5 hours. The solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with 1M citric acid solution, water and saturated brine, and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give a mixture of 7-bromo-1-(t-

butoxycarbonyl)-1,2,3,4-tetrahydro-1-benzazepin-5-one and 7-bromo-1-(t-butoxycarbonyl)-5-(t-butoxycarbonyloxy)-2,3-dihydro-1H-1-benzazepine (24.6g) as yellow oil.

<sup>1</sup>H NMR (δ ppm, CDCl<sub>3</sub>) 1.43 (4.5H, s), 1.49 (9H, s), 2.15 (1H, quint, J = 6.8 Hz), 2.76 (2H, t, J = 6.8 Hz), 3.73 (2H, t, J = 6.8 Hz), 5.97 (0.5H, t, J = 4.6 Hz), 7.17 (0.5H, br), 7.35 (1H, br), 7.54 - 7.59 (1H, m), 7.98 (0.5H, d, J = 2.6 Hz).

#### Reference Example 19

10 In dimethyl carbonate (400ml) was dissolved a mixture (3.3g) of 7-bromo-1-(t-butoxycarbonyl)-1,2,3,4-tetrahydro-1-benzazepin-5-one and 7-bromo-1-(t-butoxycarbonyl)-5-(t-butoxycarbonyloxy)-2,3-dihydro-1H-1-benzazepine. To the solution was added sodium methoxide  
15 (23.0g), and the mixture was refluxed under nitrogen atmosphere for 2.5 hours and poured into ice-water. To the mixture was added 1M citric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried  
20 with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-bromo-1-(t-butoxycarbonyl)-1,2,3,4-tetrahydro-1-benzazepin-5-one-4-carboxylate (23.8g) as yellow oil.

25 <sup>1</sup>H NMR (δ ppm, CDCl<sub>3</sub>) 1.36 (4.5H, s), 1.52 (4.5H, s), 2.43 -



2.55 (2H, m), 3.39 - 3.54 (0.5H, m), 3.72 (1.5H, s), 3.84  
(1.5H, s), 3.89 - 4.04 (2H, m), 7.12 (0.5H, br), 7.42 (0.5H,  
br), 7.51 (0.5H, dd, J = 2.2, 8.4 Hz), 7.58 (0.5H, dd, J =  
2.4, 8.6 Hz), 7.82 (0.5H, d, J = 2.2 Hz), 8.00 (0.5H, d, J  
5 = 2.2 Hz).

#### Reference Example 20

In THF (150ml) was dissolved methyl 7-bromo-1-(t-butoxycarbonyl)-1,2,3,4-tetrahydro-1-benzazepin-5-one-4-carboxylate (7.2g). To the solution was added sodium  
10 borohydride (0.7g) at -40°C, and then was added dropwise methanol (15ml). The mixture was stirred at -15°C for 1 hour. To the mixture was added 1M citric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried  
15 with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was dissolved in THF (150ml), and to the solution was added triethylamine (7.5ml). To the mixture was added dropwise, under ice-cooling, methanesulfonyl chloride (2.1ml). Under nitrogen  
20 atmosphere, the mixture was stirred at room temperature for 1.5 hours, and to the mixture was added dropwise DBU (13.5ml) at room temperature. The mixture was stirred at 90°C for 10 minutes, and the solvent was evaporated. To the residue was added water, and the mixture was  
25 extracted with ethyl acetate. The organic layer was

washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give  
5 methyl 7-bromo-1-(t-butoxycarbonyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (5.18g) as colorless crystals.  
mp 144 - 145°C.

<sup>1</sup>H NMR ( $\delta$  ppm, CDCl<sub>3</sub>) 1.47 (9H, s), 2.89 (2H, t, J = 4.8 Hz),  
3.61 (2H, br), 3.83 (3H, s), 7.27 (1H, br), 7.39 (1H, dd, J  
10 = 1.8, 8.4 Hz), 7.54 - 7.55 (2H, m).

IR (KBr)  $\nu$ : 2978, 1709 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>17</sub>H<sub>20</sub>BrNO<sub>4</sub>: C, 53.42; H, 5.27; N, 3.66.

Found C, 53.58; H, 5.12; N, 3.52.

#### Reference Example 21

15 In ethyl acetate (50ml) was dissolved methyl 7-bromo-1-(t-butoxycarbonyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.5g). To the solution was added 6N hydrochloric acid (2ml), and the mixture was heated to stir at 80°C for 2 hours, neutralized with 1N sodium  
20 hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give methyl 7-bromo-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.0g) as yellow crystals.  
25 mp 143 - 145°C.

$^1\text{H}$  NMR ( $\delta$  ppm,  $\text{CDCl}_3$ ) 2.85 (2H, t,  $J = 4.8$  Hz), 3.35 (2H, t,  $J = 4.8$  Hz), 3.80 (3H, s), 4.62 (1H, br), 6.49 (1H, d,  $J = 8.4$  Hz), 7.15 (1H, dd,  $J = 2.4, 8.4$  Hz), 7.37 (1H, d,  $J = 2.4$  Hz), 7.53 (1H, s).

5 IR (KBr)  $\nu$ : 3384, 2949, 1694  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{12}\text{H}_{12}\text{BrNO}_2$ : C, 51.09; H, 4.29; N, 4.96.

Found C, 51.17; H, 4.32; N, 4.97.

~~Reference Example 22~~

To anhydrous acetic acid (0.84ml) was added dropwise formic acid (0.4ml), under ice-cooling, and the mixture was stirred, under nitrogen atmosphere, at  $50^\circ\text{C}$  for 2 hours. To the mixture was added THF (5ml), and to the mixture was added dropwise, under ice-cooling, a solution of methyl 7-bromo-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.0g) in THF (15ml). The mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give methyl 7-bromo-1-formyl -2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.07g) as colorless crystals.  
mp  $175 - 176^\circ\text{C}$ .

25  $^1\text{H}$  NMR ( $\delta$  ppm,  $\text{CDCl}_3$ ) 2.93 (2H, t,  $J = 5.3$  Hz), 3.80 (2H, t,

Ammon.  
B28 10

J = 5.3 Hz), 3.83 (3H, s), 7.01 (1H, d J = 8.5 Hz), 7.50 (1H, dd, J = 2.2, 8.5 Hz), 7.58 (1H, s), 7.65 (1H, d, J = 2.2 Hz), 8.46 (1H, s).

IR (KBr) v: 2951, 1713, 1680  $\text{cm}^{-1}$ .

- 5     Anal. Calcd. for  $\text{C}_{13}\text{H}_{12}\text{BrNO}_3$ : C, 50.34; H, 3.90; N, 4.52.  
Found C, 50.43; H, 3.75; N, 4.45.

#### Reference Example 23

- To a mixture of methyl 7-bromo-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (3.51g), 4-  
10     morpholinophenyl borate (3.51g) and potassium carbonate (3.75g) was added a mixture of water (20ml), ethanol (20ml) and toluene (100ml), and the mixture was stirred under argon atmosphere at room temperature for 40 minutes. To the mixture was added tetrakis(triphenylphosphine)-  
15     palladium (0.52g), and the mixture was refluxed under argon atmosphere for 12 hours and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was  
20     purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 1-formyl-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (3.64g) as pale yellow crystals.  
mp 178 - 181°C.  
25      $^1\text{H}$  NMR ( $\delta$  ppm,  $\text{CDCl}_3$ ) 2.95 (2H, t, J = 5.1 Hz), 3.23 (4H, t,

J = 4.9 Hz), 3.82 - 3.92 (6H, m), 3.84 (3H, s), 6.97 - 7.04 (2H, m), 7.17 (1H, d, J = 8.2 Hz), 7.45 - 7.60 (3H, m), 7.69 (1H, d, J = 2.2 Hz), 7.76 (1H, s), 8.53 (1H, s).  
IR (KBr)  $\nu$ : 2951, 2830, 1709, 1674  $\text{cm}^{-1}$ .

5           Reference Example 24

In methanol (250ml) and THF (250ml) was dissolved methyl 1-formyl-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (3.54g). To the solution was added 1N sodium hydroxide solution (90ml), and the  
10 mixture was stirred at room temperature overnight and concentrated. To the mixture was added water, and the mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, and the solvent  
15 was evaporated to give 1-formyl-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (3.30g) as colorless crystals.  
mp 247 - 257°C (dec.).

$^1\text{H}$  NMR ( $\delta$  ppm, DMSO- $d_6$ ) 2.75 (2H, t-like) 3.14 - 3.19 (4H, m), 3.70 - 3.78 (6H, m), 7.03 (2H, d, J = 8.8 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.62 - 7.71 (4H, m), 7.87 (1H, s), 8.51 (1H, s).  
20

IR (KBr)  $\nu$ : 1671  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4 \cdot 0.7\text{H}_2\text{O}$ : C, 67.57; H, 6.03; N, 7.16.  
25 Found C, 67.48; H, 5.74; N, 6.98.

## Reference Example 25

A mixture of methyl 7-bromo-1-(t-butoxycarbonyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (2.0g), 4-morpholinophenyl borate (1.2g), and 1M potassium carbonate solution (15ml), ethanol (15ml) and toluene (100ml) was stirred under argon atmosphere at room temperature for 20 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.24g), and the mixture was refluxed under argon atmosphere for 12 hours and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 1-(t-butoxycarbonyl)-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (3.64g) as pale yellow crystals.

mp 183 - 185°C.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 1.49 (9H, s), 2.90 (2H, t,  $J = 5.0$  Hz), 3.19 - 3.24 (4H, m), 3.69 (2H, br), 3.83 (3H, s), 3.87 - 3.91 (4H, m), 6.98 (2H, d,  $J = 9.0$  Hz), 7.48 (2H, br), 7.52 (2H, d,  $J = 9.0$  Hz), 7.58 (1H, s), 7.73 (1H, s).

IR (KBr)  $\nu$ : 2973, 1705  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_5$ : C, 69.81; H, 6.94; N, 6.03.

Found C, 69.57; H, 6.76; N, 5.76.

## Reference Example 26

In ethyl acetate (100ml) was dissolved methyl 1-(t-butoxycarbonyl)-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (2.0g). To the solution was  
5 added 6N hydrochloric acid (40ml), and the mixture was stirred at 80°C for 30 minutes, neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium  
10 sulfate, and the solvent was evaporated to give 7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.46g) as yellow crystals.  
mp 175 - 182°C (dec.).  
<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 2.89 (2H, t, J = 4.5 Hz), 3.17 - 3.22  
15 (4H, m), 3.41 (2H, t, J = 4.5 Hz), 3.81 (3H, s), 3.87 - 3.91 (4H, m), 6.67 (1H, d, J = 8.3 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.33 (1H, dd, J = 2.0, 8.3 Hz), 7.45 - 7.50 (3H, m), 7.73 (1H, s).  
IR (KBr) v: 3378, 2953, 1694 cm<sup>-1</sup>.  
20 Anal. Calcd. for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>·0.2H<sub>2</sub>O: C, 71.80; H, 6.68; N, 7.61.  
Found C, 71.51; H, 6.72; N, 7.47.

## Reference Example 27

To anhydrous acetic acid (0.2ml) was added dropwise formic acid (0.1ml), under ice-cooling, and the mixture  
25 was heated to stir under nitrogen atmosphere at 50°C for

2 hours. To the mixture was added THF (5ml), and then to the mixture was added dropwise, under ice-cooling, a solution of methyl 7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g) in THF (15ml). The mixture was stirred at room temperature for 1.5 hours. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give methyl 1-formyl-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g) as pale yellow crystals.

#### Reference Example 28

A mixture of methyl 7-bromo-1-(t-butoxycarbonyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.0g), 4-ethoxyphenyl borate (0.5g), 1M potassium carbonate solution (8ml), ethanol (8ml) and toluene (50ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.12g), and the mixture was refluxed overnight under argon atmosphere and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was



evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 1-(*t*-butoxycarbonyl)-7-(4-morpholinophenyl)-2,3-dihydro-1*H*-1-benzazepine-4-

5 carboxylate (1.1g) as colorless crystals.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.38 - 1.49 (12H, m), 2.91 (2H, t, J = 5.3 Hz), 3.68 (2H, br), 3.83 (3H, s), 4.09 (2H, q, J = 7.0 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.47 - 7.55 (4H, m), 7.58 (1H, s), 7.74 (1H, 4).

10 IR (KBr) v: 2980, 1705 cm<sup>-1</sup>.

#### Reference Example 29

In ethyl acetate (50ml) was dissolved methyl 1-(*t*-butoxycarbonyl)-7-(4-ethoxyphenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (1.1g). To the solution was  
15 added 6N hydrochloric acid (10ml) and the mixture was stirred at 80°C for 40 minutes, neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium  
20 sulfate, and the solvent was evaporated to give methyl 7-(4-ethoxyphenyl)-2,3-dihydro-1*H*-1-benzazepine-4-carboxylate (0.78g) as yellow crystals.

mp 157 - 158°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.43 (3H, t, J = 7.0 Hz), 2.88 (2H, t, J = 4.6 Hz), 3.40 (2H, t, J = 4.6 Hz), 3.81 (3H, s), 4.07

(2H, q,  $J = 7.0$  Hz), 6.66 (1H, d,  $J = 8.3$  Hz), 6.94 (2H, d,  $J = 9.2$  Hz), 7.31 (1H, dd,  $J = 2.2, 8.3$  Hz), 7.41 - 7.47 (3H, m), 7.73 (1H, s).

IR (KBr)  $\nu$ : 3380, 2980, 2948, 1699  $\text{cm}^{-1}$ .

5           Reference Example 30

To anhydrous acetic acid (0.18ml) was added dropwise formic acid (0.09ml) under ice-cooling, and the mixture was stirred under nitrogen atmosphere at 50°C for 2 hours. To the mixture was added THF (2ml) and then was added dropwise, under ice-cooling a solution of methyl 7-(4-ethoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.25g) in THF (15ml), and the mixture was stirred at room temperature for 4 hours. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give methyl 7-(4-ethoxyphenyl)-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.24g) as yellow crystals.

mp 133 - 135°C.

$^1\text{H}$ -NMR ( $\delta$  ppm,  $\text{CDCl}_3$ ) 1.45 (3H, t,  $J = 6.9$  Hz), 2.95 (2H, t,  $J = 4.9$  Hz), 3.82 - 3.88 (5H, m), 4.09 (2H, q,  $J = 6.9$  Hz), 6.99 2H, d,  $J = 8.8$  Hz), 7.17 (1H, d,  $J = 8.0$  Hz), 7.49 - 7.58 (3H, m), 7.68 (1H, d,  $J = 2.2$  Hz), 7.75 (1H, s), 8.53

(1H, s).

IR (KBr) v: 2980, 2948, 1709, 1678  $\text{cm}^{-1}$ .

#### Reference Example 31

In methanol (25ml) and THF (30ml) was dissolved  
5 methyl 7-(4-ethoxyphenyl)-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.24g). To the solution was added 1N sodium hydroxide solution (5ml) and the mixture was stirred at room temperature overnight and concentrated. To the residue was added water, and the  
10 mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-(4-ethoxyphenyl)-1-formyl-2,3-  
15 dihydro-1H-1-benzazepine-4-carboxylic acid (0.23g) as pale yellow crystals.

mp 224 - 226°C.

$^1\text{H}$ -NMR ( $\delta$  ppm,  $\text{CDCl}_3$ ) 1.46 (3H, t,  $J = 6.9$  Hz), 2.97 (2H, t,  $J = 5.1$  Hz), 3.88 (2H, t,  $J = 5.1$  Hz), 4.10 (2H, q,  $J = 6.9$  Hz), 7.00 (2H, d,  $J = 8.8$  Hz), 7.20 (1H, d,  $J = 8.1$  Hz),  
20 7.53 (2H, d,  $J = 8.8$  Hz), 7.59 (1H, dd,  $J = 2.0, 8.1$  Hz), 7.70 (1H, d,  $J = 2.0$  Hz), 7.86 (1H, s), 8.56 (1H, s).

IR (KBr) v: 2982, 1669, 1682  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{20}\text{H}_{19}\text{NO}_4 \cdot 0.4\text{H}_2\text{O}$ : C, 69.71; H, 5.79; N, 4.06.

25 Found C, 69.80; H, 6.00; N, 3.80.

## Reference Example 32

A mixture of methyl 7-bromo-1-(t-butoxycarbonyl)-  
2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.0g), 4-(2-  
ethoxyethoxy)phenyl borate (0.6g), 1M potassium carbonate  
5 solution (8ml), ethanol (8ml) and toluene (50ml) was  
stirred under argon atmosphere at room temperature for 20  
minutes. To the mixture was added  
tetrakis(triphenylphosphine)palladium (0.12g), and the  
mixture was refluxed overnight under argon atmosphere and  
10 extracted with ethyl acetate. The organic layer was  
washed with water and saturated brine and dried with  
anhydrous magnesium sulfate, and the solvent was  
evaporated under reduced pressure. The residue was  
purified with silica gel column chromatography (ethyl  
15 acetate/hexane) to give methyl 1-(t-butoxycarbonyl)-7-[4-  
(2-ethoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-  
carboxylate (1.1g) as colorless oil.

<sup>1</sup>H-NMR ( $\delta$  ppm, CDCl<sub>3</sub>) 1.26 (3H, t, J = 7.1 Hz), 1.49 (9H, s),  
2.91 (2H, t, J = 4.8 Hz), 3.63 (2H, q, J = 7.1 Hz), 3.68  
20 (2H, br), 3.83 (2H, t, J = 4.9 Hz), 3.83 (3H, s), 4.17 (2H,  
t, J = 4.9 Hz), 7.00 (2H, d, J = 8.8 Hz), 7.47 - 7.53 (4H,  
m), 7.58 (1H, s), 7.73 (1H, s).

IR (neat)  $\nu$ : 2976, 1705 cm<sup>-1</sup>.

## Reference Example 33

25 In ethyl acetate (50ml) was dissolved methyl 1-(t-

10018334-124704

butoxycarbonyl)-7-[4-(2-ethoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.1g): To the solution was added 6N hydrochloric acid (20ml), and the mixture was stirred at 80°C for 45 minutes, neutralized with 1N sodium hydroxide solution and was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give methyl 7-[4-(2-ethoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.7g) as yellow crystals.

mp 102 - 108°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.26 (3H, t, J = 7.0 Hz), 2.88 (2H, t, J = 4.7 Hz), 3.40 (2H, t, J = 4.7 Hz), 3.62 (2H, q, J = 7.0 Hz), 3.81 (3H, s), 3.82 (2H, t, J = 5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.67 (1H, d, J = 8.5 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.31 (1H, dd, J = 2.2, 8.5 Hz), 7.42 - 7.47 (3H, m), 7.73 (1H, s).

IR (KBr) v: 3370, 2976, 2946, 2870, 1698 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>22</sub>H<sub>25</sub>NO<sub>4</sub>: C, 71.91; H, 6.86; N, 3.81. Found C, 71.88; H, 6.79; N, 3.78.

#### Reference Example 34

To anhydrous acetic acid (0.25ml) was added formic acid (0.13ml) under ice-cooling, and the mixture was stirred under nitrogen atmosphere at 50°C for 2 hours. To the mixture was added THF (2ml) and then was added

dropwise, under ice-cooling, a solution of methyl 7-[4-(2-ethoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.25g) in THF (10ml), and the mixture was stirred at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give methyl 7-[4-(2-ethoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.2g) as colorless crystals.

mp 138 - 142°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.27 (3H, t, J = 6.9 Hz), 2.95 (2H, t, J = 5.1 Hz), 3.63 (2H, q, J = 6.9 Hz), 3.81 - 3.88 (7H, m), 4.19 (2H, t, J = 5.0 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.17 (1H, d, J = 8.2 Hz), 7.48 - 7.59 (3H, m), 7.68 (1H, d, J = 2.2 Hz), 7.75 (1H, s).

IR (KBr) v: 2872, 1709, 1678 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>23</sub>H<sub>25</sub>NO<sub>5</sub>: C, 69.86; H, 6.37; N, 3.54. Found C, 69.88; H, 6.43; N, 3.49.

#### Reference Example 35

In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-(2-ethoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.2g). To the solution

was added 1N sodium hydroxide solution (5ml), and the mixture was stirred at room temperature overnight and concentrated. To the residue was added water, and the mixture was neutralized with 1N hydrochloric acid and  
5 extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-[4-(2-ethoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.19g) as  
10 colorless crystals.

mp 190 - 192°C.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 1.27 (3H, t,  $J = 7.0$  Hz), 2.97 (2H, t,  $J = 4.4$  Hz), 3.64 (2H, q,  $J = 7.0$  Hz), 3.81 - 3.90 (4H, m), 4.19 (2H, t,  $J = 5.0$  Hz), 7.03 (2H, d,  $J = 8.8$  Hz), 7.19  
15 (1H, d,  $J = 8.2$  Hz), 7.52 (2H, d,  $J = 8.8$  Hz), 7.59 (1H, dd,  $J = 2.2, 8.2$  Hz), 7.69 (1H, d,  $J = 2.2$  Hz), 7.85 (1H, s), 8.55 (1H, s).

IR (KBr)  $\nu$ : 2936, 2872, 1682, 1671  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{22}\text{H}_{23}\text{NO}_5$ : C, 69.28; H, 6.08; N, 3.67. Found  
20 C, 69.00; H, 6.31; N, 3.56.

#### Reference Example 36

A mixture of methyl 7-bromo-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (20g), 4-(2-ethoxyethoxy)phenyl borate (14.9g), 1M potassium  
25 carbonate solution (130ml), ethanol (130ml) and toluene

(1000ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (3g), and the mixture was refluxed under argon atmosphere for 15 hours and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-[4-(2-ethoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (25.2g) as colorless crystals.

#### Reference Example 37

A mixture of methyl 7-bromo-1-(t-butoxycarbonyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.0g), 4-(3-ethoxypropoxy)phenyl borate (0.62g), 1M potassium carbonate solution (8ml), ethanol (8ml) and toluene (50ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.12g), and the mixture was refluxed overnight under argon atmosphere and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was



purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 1-(t-butoxycarbonyl)-7-[4-(3-ethoxypropoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.2g) as colorless crystals.

5 mp 125 - 128°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.21 (3H, t, J = 7.0 Hz), 1.49 (9H, s),  
2.02 - 2.14 (2H, m), 2.91 (2H, t, J = 4.2 Hz), 3.51 (2H, q,  
J = 7.0 Hz), 3.62 (2H, t, J = 6.3 Hz), 3.65 (2H, br), 3.83  
(3H, s), 4.12 (2H, t, J = 6.2 Hz), 6.98 (2H, d, J = 8.8 Hz),  
10 7.40 - 7.55 (4H, m), 7.57 (1H, s), 7.73 (1H, s).

IR (KBr) ν: 2976, 2948, 2872, 1705 cm<sup>-1</sup>.

#### Reference Example 38

In ethyl acetate (50ml) was dissolved methyl 1-(t-butoxycarbonyl)-7-[4-(3-ethoxypropoxy)phenyl]-2,3-  
15 dihydro-1H-1-benzazepine-4-carboxylate (1.2g). To the solution was added 6N hydrochloric acid (10ml), and the mixture was stirred at 80°C for 30 minutes, neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water  
20 and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give methyl 7-[4-(3-ethoxypropoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.8g) as yellow crystals.

mp 99 - 102°C.

25 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.21 (3H, t, J = 7.0 Hz), 2.01 - 2.13

(2H, m), 2.88 (2H, t, J = 4.7 Hz), 3.41 (2H, t, J = 4.7 Hz),  
3.51 (2H, q, J = 7.0 Hz), 3.62 (2H, t, J = 6.2 Hz), 3.81  
(3H, s), 4.10 (2H, t, J = 6.2 Hz), 4.78 (1H, br), 6.67 (1H,  
d, J = 8.5 Hz), 6.95 (2H, d, J = 8.8 Hz), 7.32 (1H, dd, J =  
5 2.2, 8.5 Hz), 7.43 - 7.47 (3H, m), 7.73 (1H, s).

IR (KBr)  $\nu$ : 3374, 2949, 2868, 1699  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{23}\text{H}_{27}\text{NO}_4$ : C, 72.42; H, 7.13; N, 3.67. Found  
C, 72.24; H, 7.04; N, 3.67.

#### Reference Example 39

10 To anhydrous acetic acid (0.22ml) was added dropwise  
formic acid (0.11ml) under ice-cooling, and the mixture  
was stirred under nitrogen atmosphere at 50°C for 2 hours.  
To the mixture was added THF (2ml) and then was added  
dropwise, under ice-cooling, a solution of methyl 7-[4-  
15 (3-ethoxypropoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-  
carboxylate (0.35g) in THF (15ml), and the mixture was  
stirred at room temperature overnight. The solvent was  
evaporated, and to the residue was added water. The  
mixture was extracted with ethyl acetate. The organic  
20 layer was washed with sodium hydrogen carbonate solution,  
water and saturated brine, and dried with anhydrous  
magnesium sulfate, and the solvent was evaporated to give  
methyl 7-[4-(3-ethoxypropoxy) phenyl]-1-formyl-2,3-  
dihydro-1H-1-benzazepine-4-carboxylate (0.36g) as  
25 colorless crystals.

mp 112 - 113°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.22 (3H, t, J = 7.0 Hz), 2.03 - 2.15 (2H, m), 2.95 (2H, t, J = 4.8 Hz), 3.52 (2H, q, J = 7.0 Hz), 3.63 (2H, t, J = 6.3 Hz), 3.84 (3H, s), 3.84 (2H, t, J = 4.8 Hz), 4.13 (2H, t, J = 6.3 Hz), 7.01 (2H, d, J = 8.8 Hz), 7.17 (1H, d, J = 8.2 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.56 (1H, dd, J = 2.2, 8.8 Hz), 7.68 (1H, d, J = 2.2 Hz), 7.75 (1H, s), 8.53 (1H, s).

IR (KBr) v: 2951, 2872, 1709, 1678 cm<sup>-1</sup>.

10 Anal. Calcd. for C<sub>24</sub>H<sub>27</sub>NO<sub>5</sub>·0.2H<sub>2</sub>O: C, 69.78; H, 6.69; N, 3.39. Found C, 69.98; H, 6.79; N, 3.28.

#### Reference Example 40

In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-(3-ethoxypropoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.31g). To the solution was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at 50°C for 1.5 hours and concentrated. To the residue was added water, and the mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-[4-(3-ethoxypropoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.3g) as colorless crystals.

mp 179 - 181°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.22 (3H, t, J = 7.1 Hz), 2.03 - 2.15 (2H, m), 2.97 (2H, t, J = 5.5 Hz), 3.52 (2H, q, J = 7.1 Hz), 3.63 (2H, t, J = 6.3 Hz), 3.88 (2H, t, J = 5.5 Hz), 4.13 (2H, t, J = 6.0 Hz), 7.01 (2H, d, J = 8.8 Hz), 7.19 (1H, d, J = 8.1 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.58 (1H, dd, J = 2.0, 8.1 Hz), 7.69 (1H, d, J = 2.0 Hz), 7.85 (1H, s), 8.55 (1H, s).

IR (KBr) ν: 3036, 2870, 1682 cm<sup>-1</sup>.

10 Anal. Calcd. for C<sub>23</sub>H<sub>25</sub>NO<sub>5</sub>: C, 69.86; H, 6.37; N, 3.54. Found C, 69.64; H, 6.32; N, 3.55.

#### Reference Example 41

A mixture of methyl 7-bromo-1-(t-butoxycarbonyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.0g), 3,4-diethoxyphenyl borate (0.63g), 1M potassium carbonate solution (8ml), ethanol (8ml) and toluene (50ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.12g), and the mixture was refluxed overnight under argon atmosphere and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl

acetate/hexane) to give methyl 1-benzazepine-4-carboxylate (1.3g) as colorless crystals.

mp 168 - 173°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.45 - 1.53 (15H, m), 2.90 (2H, t, J = 5.0 Hz), 3.68 (2H, br), 3.83 (3H, s), 4.09 - 4.23 (4H, m), 6.95 (1H, d, J = 9.2 Hz), 7.09 - 7.14 (2H, m), 7.40 - 7.52 (2H, m), 7.57 (1H, s), 7.74 (1H, s).

IR (KBr) v: 2980, 1705 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>27</sub>H<sub>33</sub>NO<sub>6</sub>: C, 69.36; H, 7.11; N, 3.00. Found C, 69.17; H, 7.11; N, 2.93.

#### Reference Example 42

In ethyl acetate (50ml) was dissolved methyl 1-(t-butoxycarbonyl)-7-(3,4-diethoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.3g). To the solution was added 6N hydrochloric acid (10ml), and the mixture was stirred at 80°C for 1 hour, neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give methyl 7-(3,4-diethoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.7g) as yellow crystals.

mp 159 - 164°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.43 - 1.52 (6H, m), 2.89 (2H, t, J = 4.8 Hz), 3.41 (2H, t, J = 4.8 Hz), 3.81 (3H, s), 4.08 -

4.22 (4H, m), 6.67 (1H, d,  $J = 8.4$  Hz), 6.92 (1H, d,  $J = 9.2$  Hz), 7.03 - 7.07 (2H, m), 7.31 (1H, dd,  $J = 2.2, 8.2$  Hz), 7.45 (1H, d,  $J = 2.2$  Hz), 7.73 (1H, s).

IR (KBr)  $\nu$ : 3391, 2980, 1688  $\text{cm}^{-1}$ .

5     Anal. Calcd. for  $\text{C}_{22}\text{H}_{25}\text{NO}_4 \cdot 0.2\text{H}_2\text{O}$ : C, 71.21; H, 6.90; N, 3.77.  
Found C, 71.23; H, 6.88; N, 3.67.

#### Reference Example 43

To anhydrous acetic acid (0.22ml) was added dropwise formic acid (0.11ml) under ice-cooling, and the mixture  
10     was stirred under nitrogen atmosphere at 50°C for 2 hours. To the mixture was added THF (2ml) and then was added dropwise, under ice-cooling, a solution of methyl 7-(3,4-diethoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.35g) in THF (20ml), and the mixture was stirred  
15     at room temperature overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous  
20     magnesium sulfate, and the solvent was evaporated to give methyl 7-(3,4-diethoxyphenyl)-1-formyl-2,3-dihydro-1H-1-benzazepine-carboxylate (0.35g) as colorless crystals.  
mp 152 - 153°C.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 1.45 - 1.54 (6H, m), 2.95 (2H, t,  $J =$   
25     5.3 Hz), 3.82 - 3.88 (5H, m), 4.10 - 4.24 (4H, m), 6.97 (1H,

d,  $J = 8.8$  Hz), 7.11 - 7.19 (3H, m), 7.56 (1H, dd,  $J = 2.2$ , 8.4 Hz), 7.67 (1H, d,  $J = 2.2$  Hz), 7.76 (1H, s), 8.53 (1H, s).

IR (KBr)  $\nu$ : 2980, 1709, 1678  $\text{cm}^{-1}$ .

5     Anal. Calcd. for  $\text{C}_{23}\text{H}_{25}\text{NO}_5 \cdot 0.2\text{H}_2\text{O}$ : C, 69.23; H, 6.42; N, 3.51.  
Found C, 69.39; H, 6.39; N, 3.48.

#### Reference Example 44

In methanol (25ml) and THF (25ml) was dissolved methyl 7-(3,4-diethoxyphenyl)-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.33g). To the solution was  
10     added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature overnight and concentrated. To the residue was added water, and the mixture was neutralized with 1N hydrochloric acid and  
15     extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-(3,4-diethoxyphenyl)-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.32g) as  
20     colorless crystals.

mp 228 - 233°C (dec.).

$^1\text{H}$ -NMR ( $\delta$  ppm,  $\text{CDCl}_3$ ) 1.49 (3H, t,  $J = 7.0$  Hz), 1.50 (3H, t,  $J = 7.0$  Hz), 2.97 (2H, t,  $J = 5.5$  Hz), 3.88 (2H, t,  $J = 5.5$  Hz), 4.11 - 4.24 (4H, m), 6.97 (1H, d,  $J = 8.7$  Hz), 7.11 -  
25     7.21 (3H, m), 7.59 (1H, dd,  $J = 2.0$ , 8.7 Hz), 7.69 (1H, d,

$J = 2.0 \text{ Hz}$ ), 7.86 (1H, s), 8.55 (1H, s).

IR (KBr)  $\nu$ : 2980, 1682, 1669  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{22}\text{H}_{23}\text{NO}_5$ : C, 69.28; H, 6.08; N, 3.67. Found C, 69.31; H, 6.23; N, 3.60.

5           Reference Example 45

10           A mixture of methyl 7-bromo-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.25g), 4-(2-butoxyethoxy)phenyl borate (0.23g), 1M potassium carbonate solution (2.5ml), ethanol (2.5ml) and toluene (25ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.04g), and the mixture was refluxed overnight under argon atmosphere and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.23g) as colorless oil.

15            $^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.94 (3H, t,  $J = 7.2 \text{ Hz}$ ), 1.34 - 1.45 (2H, m), 1.55 - 1.69 (2H, m), 2.94 (2H, t,  $J = 5.0 \text{ Hz}$ ), 3.56 (2H, t,  $J = 6.6 \text{ Hz}$ ), 3.79 - 3.87 (7H, m), 4.18 (2H, t,  $J = 5.0 \text{ Hz}$ ), 7.02 (2H, d,  $J = 9.2 \text{ Hz}$ ), 7.17 (1H, d,  $J = 8.4$

20           

25



Hz), 7.48 - 7.58 (3H, m), 7.68 (1H, d,  $J = 2.2$  Hz), 7.75 (1H, s), 8.53 (1H, s).

IR (neat)  $\nu$ : 2938, 2870, 1713, 1682  $\text{cm}^{-1}$ .

~~Reference Example 46~~

Ammon.  
B29

5 In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.23g). To the solution was added 1N sodium hydroxide solution (5ml), and the mixture was stirred at 55°C for 1.5 hours and

10 concentrated. To the residue was added water, and the mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was

15 evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.24g) as colorless amorphous.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.94 (3H, t,  $J = 7.3$  Hz), 1.27 - 1.45 (2H, m), 1.55 - 1.66 (2H, m), 2.97 (2H, t,  $J = 4.9$  Hz),

20 3.57 (2H, t,  $J = 6.8$  Hz), 3.80 - 3.90 (4H, m), 4.18 (2H, t,  $J = 4.9$  Hz), 7.06 (2H, d,  $J = 8.8$  Hz), 7.19 (1H, d,  $J = 8.2$  Hz), 7.52 (2H, d,  $J = 8.8$  Hz), 7.58 (1H, dd,  $J = 2.0, 8.2$  Hz), 7.69 (1H, d,  $J = 2.0$  Hz), 7.85 (1H, s), 8.55 (1H, s).

IR (KBr)  $\nu$ : 2955, 2934, 2867, 1682, 1669  $\text{cm}^{-1}$ .

25 Reference Example 47

A mixture of methyl 7-bromo-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.2g), 4-[N-(2-ethoxyethyl)-N-methylamino]phenyl borate (0.17g), potassium carbonate (0.2g), water (1.1ml), ethanol (1.1ml) and toluene (10.7ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.03g), and the mixture was refluxed overnight under argon atmosphere and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-[4-[N-(2-ethoxyethyl)-N-methylamino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.22g) as colorless amorphous. <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.21 (3H, t, J = 7.0 Hz), 2.91 - 2.97 (2H, m), 3.05 (3H, s), 3.52 (2H, q, J = 7.0 Hz), 3.58 - 3.63 (4H, m), 3.81 - 3.88 (2H, m), 3.84 (3H, s), 6.81 (2H, d, J = 8.8 Hz), 7.14 (1H, d, J = 8.2 Hz), 7.46 - 7.57 (3H, m), 7.67 (1H, d, J = 2.0 Hz), 7.75 (1H, s), 8.52 (1H, s). IR (KBr) ν: 1707, 1678, 1610, 1503, 1358, 1261, 1234, 1196 cm<sup>-1</sup>.

#### Reference Example 48

In methanol (6.6ml) and THF (4.4ml) was dissolved

methyl 7-[4-[N-(2-ethoxyethyl)-N-methylamino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.22g). To the solution was added 1N sodium hydroxide solution (2.2ml), and the mixture was stirred at room temperature overnight and concentrated. To the residue was added water, and the mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-[4-[N-(2-ethoxyethyl)-N-methylamino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.18g) as colorless amorphous.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 1.10 (3H, t,  $J = 7.4$  Hz), 2.68 - 2.81 (2H, m), 2.97 (3H, s), 3.26 - 3.38 (2H, m), 3.44 (2H, q,  $J = 7.0$  Hz), 3.54 (3H, s), 3.68 - 3.73 (2H, m), 6.79 (2H, d,  $J = 8.8$  Hz), 7.36 (1H, d,  $J = 8.8$  Hz), 7.56 - 7.73 (4H, m), 7.86 (1H, s), 8.52 (1H, s).

IR (KBr)  $\nu$ : 2975, 2876, 1678, 1611, 1503, 1312, 1431, 1292, 1273, 1194, 1117, 810  $\text{cm}^{-1}$ .

#### Reference Example 49

A mixture of methyl 7-bromo-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.2g), 4-[N-(2-ethoxyethyl)-N-ethylamino]phenyl borate (0.46g), 1M potassium carbonate solution (3.2ml), ethanol (3.2ml) and toluene

(25ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.03g), and the mixture was refluxed overnight under argon atmosphere and  
5 extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl  
10 acetate/hexane) to give methyl 7-[4-[N-(2-ethoxyethyl)-N-ethylamino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.23g) as green amorphous.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.17 - 1.26 (6H, m), 2.94 (2H, t, J = 4.8 Hz), 3.42 - 3.64 (8H, m), 3.82 - 3.87 (5H, m), 6.78 (2H,  
15 d, J = 8.8 Hz), 7.13 (1H, d, J = 8.1 Hz), 7.47 (2H, d, J = 8.8 Hz), 7.54 (1H, dd, J = 2.1, 8.1 Hz), 7.66 (1H, d, J = 2.1 Hz), 7.75 (1H, s), 8.51 (1H, s).

IR (KBr) ν: 2973, 2868, 1709, 1678 cm<sup>-1</sup>.

#### Reference Example 50

20 In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-[N-(2-ethoxyethyl)-N-ethylamino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.23g). To the solution was added 1N sodium hydroxide solution (5.5ml), and the mixture was stirred at room temperature  
25 overnight and concentrated. To the residue was added

water, and the mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-[4-[N-(2-ethoxyethyl)-N-ethylamino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.2g) as pale green crystals.

mp 182 - 184°C.

<sup>1</sup>H-NMR ( $\delta$  ppm, CDCl<sub>3</sub>) 1.17 - 1.30 (6H, m), 2.97 (2H, t, J = 5.7 Hz), 3.43 - 3.65 (8H, m), 3.87 (2H, t, J = 5.7 Hz), 6.79 (2H, d, J = 8.8 Hz), 7.16 (1H, d, J = 8.4 Hz), 7.48 (2H, d, J = 8.8 Hz), 7.58 (1H, dd, J = 2.0, 8.4 Hz), 7.68 (1H, d, J = 2.0 Hz), 7.86 (1H, s), 8.54 (1H, s).

IR (KBr)  $\nu$ : 2973, 2872, 1682 cm<sup>-1</sup>.

#### Reference Example 51

A mixture of methyl 7-bromo-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.25g), 4-[N-ethyl-N-(2-propoxyethyl)amino]phenyl borate (0.3g), 1M potassium carbonate solution (2.5ml), ethanol (2.5ml) and toluene (25ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.04g), and the mixture was refluxed overnight under argon atmosphere and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with

anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-[4-[N-ethyl-N-(2-propoxyethyl)amino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.31g) as green oil.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.21 (3H, t, J = 7.0 Hz), 1.59 - 1.66 (2H, m), 2.94 (2H, t, J = 5.2 Hz), 3.39 - 3.64 (8H, m), 3.82 - 3.87 (5H, m), 6.78 (2H, d, J = 9.0 Hz), 7.14 (1H, d, J = 8.2 Hz), 7.47 (2H, d, J = 9.0 Hz), 7.55 (1H, dd, J = 2.0, 8.2 Hz), 7.66 (1H, d, J = 2.0 Hz), 7.75 (1H, s), 8.52 (1H, s).

IR (neat) ν: 2942, 2867, 1709, 1682 cm<sup>-1</sup>.

#### Reference Example 52

In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-[N-ethyl-N-(2-propoxyethyl)amino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.31g). To the solution was added 1N sodium hydroxide solution (7ml), and the mixture was stirred at 60°C for 1.5 hours and concentrated. To the residue was added water, and the mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-[4-[N-ethyl-N-(2-

propoxyethyl)amino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.29g) as pale yellow crystals.

mp 169 - 171°C.

5 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.5 Hz), 1.21 (3H, t, J = 7.0 Hz), 1.56 - 1.66 (2H, m), 2.96 (2H, t, J = 5.0 Hz), 3.39 - 3.62 (8H, m), 3.87 (2H, t, J = 5.0 Hz), 6.78 (2H, d, J = 8.8 Hz), 7.16 (1H, d, J = 8.0 Hz), 7.47 (2H, d, J = 8.8 Hz), 7.58 (1H, dd, J = 2.0, 8.0 Hz), 7.68 (1H, d, J = 2.0 Hz), 7.84 (1H, s), 8.54 (1H, s).

10 IR (KBr) v: 2967, 2870, 1680 cm<sup>-1</sup>.

#### Reference Example 53

In THF (50ml) were dissolved methyl 7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.7g) and pyridine (1.2ml). To the solution was added methanesulfonic anhydride (1.5g), and the mixture was stirred under nitrogen atmosphere at 50 for 3 hours. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-methanesulfonyl-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-

15

20

25

carboxylate (0.4g) as pale yellow crystals.

mp 224 - 226°C (dec.).

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 2.78 (3H, s), 3.05 (2H, t, J = 5.0 Hz),  
3.21 - 3.26 (4H, m), 3.85 - 3.92 (9H, m), 6.99 (2H, d, J =  
5 9.2 Hz), 7.50 - 7.58 (3H, m), 7.63 - 7.69 (2H, m), 7.80 (1H,  
s).

IR (KBr) v: 2953, 1709 cm<sup>-1</sup>.

#### Reference Example 54

In methanol (100ml) and THF (100ml) was dissolved  
10 methyl 1-methanesulfonyl-7-(4-morpholinophenyl)-2,3-  
dihydro-1H-1-benzazepine-4-carboxylate (0.4g). To the  
solution was added 1N sodium hydroxide solution (10ml),  
and the mixture was stirred at room temperature overnight.  
To the mixture was added 1N sodium hydroxide solution  
15 (5ml), and the mixture was stirred at 60°C for 1.5 hours  
and concentrated. To the residue was added water, and  
the mixture was neutralized with 1N hydrochloric acid and  
extracted with ethyl acetate. The organic layer was  
washed with water and saturated brine and dried with  
20 anhydrous magnesium sulfate, and the solvent was  
evaporated to give 1-methanesulfonyl-7-(4-  
morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-  
carboxylic acid (0.36g) as pale yellow crystals.  
mp 264 - 275°C (dec.).

25 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub> + CD<sub>3</sub>OD) 2.79 (3H, s), 3.02 (2H, t, J =



5.1 Hz), 3.21 - 3.26 (4H, m), 3.84 - 3.92 (6H, m), 7.00 (2H, d,  $J = 8.8$  Hz), 7.50 - 7.58 (3H, m), 7.64 - 7.68 (2H, m), 7.83 (1H, s).

IR (KBr)  $\nu$ : 2969, 2832, 1671  $\text{cm}^{-1}$ .

5     Anal. Calcd. for  $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$ : C, 61.66; H, 5.65; N, 6.54.  
Found C, 61.48; H, 5.81; N, 6.25.

#### Reference Example 55

In THF (25ml) were dissolved methyl 7-(4-ethoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate  
10     (0.25g) and pyridine (0.6ml). To the solution was added  
methanesulfonic anhydride (0.67g), and the mixture was  
stirred under nitrogen atmosphere at 40°C overnight. To  
the mixture was added methanesulfonic anhydride (0.13g),  
and the mixture was stirred at 40°C for 4 hours. The  
15     solvent was evaporated. To the residue was added water,  
and the mixture was extracted with ethyl acetate. The  
organic layer was washed with water and saturated brine  
and dried with anhydrous magnesium sulfate, and the  
solvent was evaporated. The residue was purified with  
20     silica gel column chromatography (ethyl acetate/hexane)  
to give methyl 7-(4-ethoxyphenyl)-1-methanesulfonyl-2,3-  
dihydro-1H-1-benzazepine-4-carboxylate (0.14g) as pale  
yellow crystals.

mp 175 - 181°C.

25      $^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 1.45 (3H, t,  $J = 7.1$  Hz), 2.78 (3H, s),

3.05 (2H, t,  $J = 4.9$  Hz), 3.84 - 3.89 (5H, m), 4.09 (2H, q,  $J = 7.1$  Hz), 6.98 (2H, d,  $J = 8.8$  Hz), 7.49 - 7.57 (3H, m), 7.63 (1H, d,  $J = 2.2$  Hz), 7.67 (1H, d,  $J = 8.4$  Hz), 7.80 (1H, s).

5 IR (KBr)  $\nu$ : 2984, 1711  $\text{cm}^{-1}$ .

Reference Example 56

In methanol (25ml) and THF (25ml) was dissolved methyl 7-(4-ethoxyphenyl)-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.14g). To the solution  
10 was added 1N sodium hydroxide solution (3ml), and the mixture was stirred at room temperature overnight and concentrated. To the residue was added water, and the mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was  
15 washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-(4-ethoxyphenyl)-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.13g) as pale yellow crystals.  
20 mp 237 - 242°C (dec.).

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 1.46 (3H, t,  $J = 7.0$  Hz), 2.81 (3H, s), 3.08 (2H, t,  $J = 5.9$  Hz), 3.89 (2H, t,  $J = 5.9$  Hz), 4.10 (2H, q,  $J = 7.0$  Hz), 6.99 (2H, d,  $J = 8.8$  Hz), 7.52 (2H, d,  $J = 8.8$  Hz), 7.58 (1H, dd,  $J = 2.0, 8.4$  Hz), 7.65 (1H, d,  $J = 2.0$  Hz), 7.70 (1H, d,  $J = 8.4$  Hz), 7.91 (1H, s).

25

IR (KBr)  $\nu$ : 2984, 1669  $\text{cm}^{-1}$ .

Reference Example 57

In THF (30ml) were dissolved methyl 7-[4-(2-ethoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.25g) and pyridine (0.5ml). To the solution was added methanesulfonic anhydride (0.6g), and the mixture was stirred under nitrogen atmosphere at 50°C overnight. To the mixture was added methanesulfonic anhydride (0.1g), and the mixture was stirred at 50°C for 2 hours. The solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-[4-(2-ethoxyethoxy)phenyl]-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.13g) as pale yellow crystals. mp 143 - 146°C.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 1.27 (3H, t,  $J = 6.9$  Hz), 2.78 (3H, s), 3.06 (2H, t,  $J = 5.2$  Hz), 3.63 (2H, q,  $J = 6.9$  Hz), 3.81 - 3.89 (7H, m), 4.19 (2H, t,  $J = 4.9$  Hz), 7.03 (2H, d,  $J = 8.8$  Hz), 7.49 - 7.57 (3H, m), 7.64 (1H, d,  $J = 2.0$  Hz), 7.68 (1H, d,  $J = 8.4$  Hz), 7.81 (1H, s).

IR (KBr)  $\nu$ : 2932, 2872, 1709  $\text{cm}^{-1}$ .

## Reference Example 58

In methanol (20ml) and THF (20ml) was dissolved methyl 7-[4-(2-ethoxyethoxy)phenyl]-1-methanesulfonyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.13g). To the solution was added 1N sodium hydroxide solution (3ml), and the mixture was stirred at room temperature overnight and concentrated. To the residue was added water, and the mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-[4-(2-ethoxyethoxy)phenyl]-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.12g) as pale yellow crystals.

mp 222 - 225°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.27 (3H, t, J = 7.1 Hz), 2.81 (3H, s), 3.08 (2H, t, J = 5.1 Hz), 3.63 (2H, q, J = 7.1 Hz), 3.81 - 3.91 (4H, m), 4.19 (2H, t, J = 4.8 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.57 (1H, dd, J = 2.2, 9.0 Hz), 7.64 (1H, d, J = 2.2 Hz), 7.67 (1H, d, J = 9.0 Hz), 7.90 (1H, s).

IR (KBr) v: 2978, 2872, 1694, 1669 cm<sup>-1</sup>.

## Reference Example 59

In THF (35ml) were dissolved methyl 7-[4-(3-ethoxypropoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-

carboxylate (0.4g) and pyridine (0.75ml). To the solution was added methanesulfonic anhydride (0.92g), and the mixture was stirred under nitrogen atmosphere at room temperature overnight. To the mixture was added

5 methanesulfonic anhydride (0.25g), and the mixture was stirred at 50°C overnight. The solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with

10 anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-[4-(3-ethoxypropoxy)phenyl]-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.26g) as

15 pale yellow crystals.

mp 127 - 129°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.22 (3H, t, J = 7.0 Hz), 2.02 - 2.15 (2H, m), 2.78 (3H, s), 3.05 (2H, t, J = 5.5 Hz), 3.51 (2H, q, J = 7.0 Hz), 3.62 (2H, t, J = 6.2 Hz), 3.85 (3H, s),

20 3.86 (2H, t, J = 5.5 Hz), 4.12 (2H, t, J = 6.2 Hz), 7.00 (2H, d, J = 8.8 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.55 (1H, dd, J = 2.2, 8.4 Hz), 7.63 (1H, d, J = 2.2 Hz), 7.67 (1H, d, J = 8.4 Hz), 7.80 (1H, s).

IR (KBr) v: 2951, 2872, 1711 cm<sup>-1</sup>.

In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-(3-ethoxypropoxy)phenyl]-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.22g). To the solution was added 1N sodium hydroxide solution (5ml), and the mixture was stirred at room temperature overnight and concentrated. To the residue was added water, and the mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-[4-(3-ethoxypropoxy)phenyl]-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.23g) as pale yellow crystals.

mp 210 - 212°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.22 (3H, t, J = 7.2 Hz), 2.03 - 2.15 (2H, m), 2.81 (3H, s), 3.08 (2H, t, J = 5.5 Hz), 3.52 (2H, q, J = 7.2 Hz), 3.63 (2H, t, J = 6.0 Hz), 3.89 (2H, t, J = 5.5 Hz), 4.13 (2H, t, J = 6.2 Hz), 7.00 (2H, d, J = 8.8 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.57 (1H, dd, J = 1.8, 8.4 Hz), 7.65 (1H, d, J = 1.8 Hz), 7.69 (1H, d, J = 8.4 Hz), 7.91 (1H, s).

IR (KBr) v: 3036, 2870, 1671 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>23</sub>H<sub>27</sub>NO<sub>6</sub>S: C, 62.00; H, 6.11; N, 3.14.

Found C, 62.17; H, 5.99; N, 3.17.

Reference Example 61

In dimethyl carbonate (15ml) was dissolved 7-bromo-1,2,3,4-tetrahydro-1-benzazepin-5-one (0.68g). To the solution was added sodium methoxide (0.92g), and the mixture was refluxed under nitrogen atmosphere for 8 hours and poured into ice-water. To the mixture was added 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give pale yellow oil (0.88g), which was dissolved in THF (30ml). To the solution was added sodium borohydride (0.1g) at -40°C and then was added dropwise methanol (3ml), and the mixture was stirred at -15°C for 1 hour. To the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was dissolved in THF (25ml), and to the solution was added triethylamine (0.7ml), and then was added dropwise, under ice-cooling, methanesulfonyl chloride (0.6ml). Under nitrogen atmosphere, the mixture was stirred at room temperature overnight, and to the mixture was added dropwise DBU (2.5ml) at room temperature. The mixture

was refluxed for 30 minutes, and the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-bromo-1-methoxycarbonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g) as colorless crystals.

mp 135 - 136°C.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 2.92 (2H, t,  $J = 5.1$  Hz), 3.70 (2H, br), 3.74 (3H, s), 3.82 (3H, s), 7.26 (1H, br), 7.42 (1H, dd,  $J = 2.2, 8.4$  Hz), 7.56 - 7.57 (2H, m).

IR (KBr)  $\nu$ : 2951, 1713  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{14}\text{H}_{14}\text{BrNO}_4$ : C, 49.43; H, 4.15; N, 4.12. Found C, 49.53; H, 4.08; N, 4.06.

#### Reference Example 62

A mixture of methyl 7-bromo-1-methoxycarbonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g), 4-morpholinophenyl borate (0.22g), 1M potassium carbonate solution (2.5ml), ethanol (2.5ml) and toluene (25ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.04g), and the mixture was refluxed overnight under argon atmosphere and



extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 1-methoxycarbonyl-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.31g) as pale yellow crystals.

mp 216 - 220°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 2.94 (2H, t, J = 5.4 Hz), 3.20 - 3.25 (4H, m), 3.75 (2H, br), 3.76 (3H, br), 3.83 (3H, s), 3.87 - 3.92 (4H, m), 6.99 (2H, d, J = 9.0 Hz), 7.39 (1H, br), 7.50 - 7.55 (3H, m), 7.60 (1H, s), 7.73 (1H, s).

IR (KBr) ν: 2953, 1713 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>·0.2H<sub>2</sub>O: C, 67.65; H, 6.25; N, 6.57. Found C, 67.50; H, 6.10; N, 6.58.

#### Reference Example 63

In methanol (40ml) and THF (60ml) was dissolved methyl 1-methoxycarbonyl-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.31g). To the solution was added 1N sodium hydroxide solution (5ml), and the mixture was stirred at room temperature overnight. To the mixture was added 1N sodium hydroxide solution (2.5ml), and the mixture was stirred at room temperature overnight and concentrated. The residue was neutralized

with 1N hydrochloric acid, precipitated crystals were filtered and washed with water to give 1-methoxycarbonyl-7-(4-morpholinophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.29g) as colorless crystals.

5 mp 274 - 279°C (dec.).

<sup>1</sup>H-NMR (δ ppm, DMSO-d<sub>6</sub>) 2.78 (2H, t-like), 3.16 - 3.18 (4H, m), 3.60 (2H, br), 3.66 (3H, s), 3.75 - 3.77 (4H, m), 7.03 (2H, d, J = 8.6 Hz), 7.40 (1H, d, J = 8.4 Hz), 7.58 - 7.69 (4H, m), 7.79 (1H, s), 12.65 (1H, br).

10 IR (KBr) v: 2969, 1705, 1678 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>·0.5H<sub>2</sub>O: C, 66.17; H, 6.04; N, 6.71.

Found C, 66.15; H, 5.74; N, 6.68.

#### Reference Example 64

In pyridine (10.0ml) were dissolved ethyl 4-(4-bromo-2-formylphenyl)aminobutyrate (3.16g) and tosyl  
15 chloride (2.88g), and the mixture was stirred at 50°C for 62 hours. The mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid and saturated brine, and the organic layer was dried with anhydrous magnesium  
20 sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (150g, hexane : ethyl acetate = 6 : 1 → 4:1) to give ethyl 4-(4-bromo-2-formylphenyl)-4-[(4-methylphenyl)sulfonyl]aminobutyrate (1.47g, 31%) as brown  
25 oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.23 (3H, t, J = 7.0 Hz), 1.77 (2H, quint, J = 7.2 Hz), 2.35 (2H, t, J = 7.1 Hz), 2.45 (3H, s), 3.27 - 3.38 (1H, m), 3.88 - 3.96 (1H, m), 4.09 (2H, q, J = 6.9 Hz), 6.60 (1H, d, J = 8.6 Hz), 7.29 (2H, d, J = 9.2 Hz), 7.44 (2H, d, J = 8.4 Hz), 7.59 (1H, dd, J = 8.5, 2.5 Hz), 8.15 (1H, d, J = 2.6 Hz), 10.35 (1H, s).

IR (KBr) 1732, 1694, 1474, 1377, 1350, 1184, 1163, 723, 655, 579 cm<sup>-1</sup>.

#### Reference Example 65

10 In a mixture of t-butanol and toluene (1:10, v/v, 66.0ml) was dissolved ethyl 4-(4-bromo-2-formylphenyl)-4-[(4-methylphenyl)sulfonyl]aminobutyrate (1456mg). To the solution was added at room temperature potassium t-butoxide (384mg), and the mixture was stirred at 100°C  
15 for 1 hour. To the mixture was added 1N hydrochloric acid to convert weakly acidic solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was  
20 evaporated under reduced pressure. The residue was purified with silica gel column chromatography (75g, hexane : ethyl acetate = 6 : 1) to give ethyl 7-bromo-1-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (413mg, 30%) as yellow amorphous.  
25 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.29 (3H, t, J = 7.2 Hz), 2.35 (3H,

s), 2.86 (2H, td,  $J = 5.8, 1.4$  Hz), 3.87 (2H, t,  $J = 6.1$  Hz), 4.19 (2H, q,  $J = 7.1$  Hz), 7.13 (2H, d,  $J = 8.0$  Hz), 7.15 - 7.19 (1H, m), 7.39 - 7.55 (5H, m).

IR (KBr) 1709, 1485, 1350, 1246, 1194, 1163, 1090, 710, 696,

5 662  $\text{cm}^{-1}$ .

#### Reference Example 66

In a mixture of water : ethanol : toluene (1 : 1 : 10 v/v, 18.0ml) were dissolved 4-(4-morpholino)phenyl borate (278mg) and ethyl 7-bromo-1-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (403mg). To the solution was added potassium carbonate (297mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium  
10 (41mg), and the mixture was refluxed under argon atmosphere for 13 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced  
15 pressure. The residue was purified with silica gel column chromatography (45g, hexane : ethyl acetate = 4 : 1  $\rightarrow$  3 : 1) to give ethyl 7-[(4-methylphenyl)sulfonyl]-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (460mg, 96%) as yellow crystals.

25  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.30 (3H, t,  $J = 7.2$  Hz), 2.34 (3H,

s), 2.87 (2H, t, J = 5.3 Hz), 3.23 (4H, t, J = 4.9 Hz),  
3.90 (4H, t, J = 4.8 Hz), 3.90 - 3.95 (2H, m), 4.20 (2H, q,  
J = 7.1 Hz), 6.99 (2H, d, J = 9.0 Hz), 7.12 (2H, d, J = 8.2  
Hz), 7.36 (1H, s), 7.45 (2H, d, J = 8.4 Hz), 7.53 (2H, d, J  
5 = 8.6 Hz), 7.46 - 7.68 (3H, m).

IR (KBr) 1705, 1609, 1493, 1348, 1233, 1161, 1123, 1092,  
932, 818, 671  $\text{cm}^{-1}$ .

#### Reference Example 67

In THF (10.0ml) was dissolved methyl 7-[4-(4-  
10 morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-  
carboxylate (369mg), and to the solution were added  
pyridine (0.11ml) and acetyl chloride (0.086ml) at room  
temperature or at 0°C. The mixture was stirred at room  
temperature for 30 minutes, and diluted with ethyl  
15 acetate and washed with water and saturated brine. The  
organic layer was dried with anhydrous magnesium sulfate,  
and the solvent was evaporated under reduced pressure to  
give methyl 1-acetyl-7-[4-(4-morpholino)phenyl]-2,3-  
dihydro-1H-1-benzazepine-4-carboxylate (400mg, 97%) as  
20 pale yellow amorphous.

$^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.05 (3H, s), 2.74 - 3.19 (3H, m),  
3.24 (4H, t, J = 4.8 Hz), 3.83 (3H, s), 3.90 (4H, t, J =  
4.8 Hz), 4.73 - 4.85 (1H, m), 7.01 (2H, d, J = 8.8 Hz),  
7.23 (1H, d, J = 8.2 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.51 -  
25 7.56 (1H, m), 7.67 (1H, d, J = 1.8 Hz), 7.74 (1H, s).

IR (KBr) 1709 ,1659, 1609, 1497, 1389, 1233, 1123  $\text{cm}^{-1}$ .

~~Reference Example 68~~

In a mixture of THF and ethanol (1:1,v/v, 10.0ml) was dissolved methyl 1-acetyl-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (394mg). To the solution was added 1N sodium hydroxide solution (3.0ml), and the mixture was stirred at room temperature for 12 hours. To the mixture was added 1N hydrochloric acid to convert weakly acidic solution, and the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 1-acetyl-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (372mg, 98%) as pale yellow crystals.

$^1\text{H-NMR}$  (200 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.95 (3H, s), 2.75 (3H, br), 3.17 (4H, t,  $J = 4.7$  Hz), 3.76 (4H, t,  $J = 4.8$  Hz), 4.54 (1H, br), 7.03 (2H, d,  $J = 8.8$  Hz), 7.46 (1H, d,  $J = 8.2$  Hz), 7.63 - 7.72 (4H, m), 7.88 (1H, s).

Reference Example 69

In THF (500ml) was dissolved methyl anthranilate (247.8g, 130mol). To the solution were added pyridine (205.7g, 2.60ml) and tosyl chloride (260.2g, 1.37mol) at room temperature, and the mixture was stirred for 14.5 hours (overnight). To the mixture were added ethyl acetate and water to carry out extraction, and the

Ammon.  
B30

10018321-121201

organic layer was washed with 1N hydrochloric acid, water and saturated brine, and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crystals which were washed with ethyl acetate and IPE (isopropyl ether) to give white crystals of methyl N-tosylanthranylate (348.0g). The mother liquor was treated by the same procedure to give methyl N-tosylanthranylate (32.4g).

Yield, 380.4 g (96%).

mp 111 - 112°C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 200 MHz)  $\delta$  2.36 (3H, s), 3.88 (3H, s), 7.03 (1H, td,  $J = 7.6, 1.7$  Hz), 7.22 (2H, d,  $J = 8.0$  Hz), 7.45 (1H, td,  $J = 7.9, 1.5$  Hz), 7.67 - 7.78 (1H, m), 7.75 (2H, d,  $J = 8.4$  Hz), 7.92 (1H, dd,  $J = 8.0, 1.6$  Hz), 10.63 (1H, brs).

IR (KBr) 3173, 1688, 1493, 1260, 1161, 1090, 567  $\text{cm}^{-1}$ .

#### Reference Example 70

In 85% acetic acid solution (1000ml) were suspended methyl N-tosylanthranylate (100g, 328mmol) and sodium acetate (29.6g, 361mmol). To the solution was added dropwise at room temperature a solution of bromine (21.0ml, 408mmol) in 85% acetic acid solution (100ml), and the mixture was stirred at 70°C for 2 hours. To the mixture was added sodium thiosulfate pentahydrate at room temperature, and excess bromine was reduced. The mixture

was concentrated under reduced pressure, and to the residue were added water and ethyl acetate. The separated organic layer was washed with potassium carbonate solution and saturated brine and dried with anhydrous magnesium sulfate. Under reduced pressure, the solvent was evaporated to give crystals, which were washed with IPE to give white crystals of methyl 5-bromo-N-tosylanthranylate (116.9g). The mother liquor was treated by the same procedure to give methyl 5-bromo-N-tosylanthranylate (6.9g). Yield, 123.5g (98%).

mp 123 - 124°C.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 200 MHz) δ 2.38 (3H, s), 3.89 (3H, s), 7.24 (2H, d, J = 9.2 Hz), 7.53 (1H, dd, J = 8.8, 2.2 Hz), 7.61 (1H, d, J = 8.6 Hz), 7.73 (2H, d, J = 8.0 Hz), 8.03 (1H, d, J = 2.2 Hz), 10.52 (1H, brs).

#### Reference Example 71

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v. 42.0ml) were dissolved 4-propoxyphenyl borate (746mg) and methyl 7-bromo-1-(t-butoxycarbonyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1320mg). To the solution was added potassium carbonate (1145mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (160mg), and the



*Amen.*  
*B 31*

mixture was heated to reflux under argon atmosphere for 14.5 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate.

5 The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (75g, hexane : ethyl acetate = 3 : 1) to give methyl 1-(t-butoxycarbonyl)-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate as yellow

10 amorphous. The obtained methyl 1-(t-butoxycarbonyl)-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate was dissolved in ethyl acetate (80ml). To the solution was added 6N hydrochloric acid (20ml) at room temperature, and the mixture was stirred at 100°C

15 for 30 minutes and neutralized with 1N sodium hydroxide and saturated sodium hydrogen carbonate solution. The separated organic layer was washed with saturated sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent

20 was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give methyl 7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (947mg) as yellow crystals. The mother liquor was concentrated, and the residue was purified

25 with silica gel column chromatography (15g, hexane:ethyl

acetate=4:1) to give desired product (147mg).

Yield, 1094mg (94%).

mp 134 - 137°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.05 (3H, t, J = 8.1 Hz), 1.83 (2H, sextet, J = 7.0 Hz), 2.88 (2H, t, J = 4.4 Hz), 3.40 (2H, t, J = 4.8 Hz), 3.81 (3H, s), 3.96 (2H, t, J = 6.6 Hz), 6.67 (1H, d, J = 8.4 Hz), 6.90 - 6.98 (2H, m), 7.32 (1H, dd, J = 8.4, 2.2 Hz), 7.45 (2H, d, J = 8.4 Hz), 7.46 (1H, d, J = 1.8 Hz), 7.73 (1H, s).

IR (KBr) 3384, 2963, 1698, 1609, 1499, 1269, 1242, 1209, 1177, 818 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>21</sub>H<sub>23</sub>NO<sub>3</sub> (0.1H<sub>2</sub>O additive): C, 74.36; H, 6.89; N, 4.13. Found C, 74.31; H, 6.81; N, 4.10.

#### Reference Example 72

To anhydrous acetic acid (0.65ml) was added formic acid (0.32ml) at 0°C, and the mixture was stirred at 60°C for 2 hours, air-cooled and diluted with THF (10ml). In THF (10ml) was dissolved methyl 7-(4 propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (520mg), and the solution was added dropwise to the previously prepared solution of formic anhydride in THF, at 0°C. The mixture was stirred at room temperature for 1.5 hours. The solvent was evaporated under reduced pressure, and the residue was diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution, water and

saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give methyl 1-formyl-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (563mg) as white crystals.

mp 151.5 - 153°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.07 (3H, t, J = 7.5 Hz), 1.85 (2H, sextet, J = 7.1 Hz), 2.92 (2H, t, J = 5.1 Hz), 3.84 (3H, s), 3.85 (2H, t, J = 5.5 Hz), 3.98 (2H, t, J = 6.6 Hz), 6.98 - 7.02 (2H, m), 7.17 (1H, d, J = 8.0 Hz), 7.48 - 7.54 (2H, m), 7.56 (1H, dd, J = 8.2, 2.2 Hz), 7.68 (1H, d, J = 2.0 Hz), 7.76 (1H, s), 8.53 (1H, s).

IR (KBr) 1709, 1678, 1497, 1358, 1236, 1192, 824 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>22</sub>H<sub>23</sub>NO<sub>4</sub>: C, 72.31; H, 6.34; N, 3.83. Found C, 72.35; H, 6.45; N, 3.83.

#### Reference Example 73

In THF (15.0ml) was dissolved methyl 7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (431mg). To the solution was added pyridine (1.0ml) and then was added a solution of methanesulfonic anhydride (1.11g) in THF (5.0 ml), at room temperature, and the mixture was stirred at 50°C for 15 hours. The mixture was diluted with ethyl acetate, and washed with water, 1N hydrochloric acid, water and saturated brine, and the

organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate to give methyl 1-methylsulfonyl-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (238mg) as white crystals. The mother liquor was concentrated, and the residue was purified with silica gel column chromatography (15g, hexane : ethyl acetate = 2 : 1) to give desired product. The obtained methyl 1-methylsulfonyl-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate was collected and dissolved in a mixture of THF and ethanol (1 : 1, v/v, 40ml). To the solution was added 1N sodium hydroxide solution (14.0ml), and the mixture was stirred at room temperature for 18 hours. The mixture was a little concentrated, and to the residue was added 1N hydrochloric acid to convert weakly acidic solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give 1-methylsulfonyl-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (273mg, 53%) as white crystals.

mp 261 - 263°C (dec.).

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 1.00 (3H, t, J = 7.3 Hz), 1.76 (2H, sextet, J = 7.0 Hz), 2.91 (2H, t-like), 3.08 (3H, s), 3.71 (2H, t-like), 3.98 (2H, t, J = 6.6 Hz), 7.02 (2H, d, J = 8.6 Hz), 7.51 (1H, d, J = 8.4 Hz), 7.61 - 7.65 (1H, m),  
5 7.67 (2H, d, J = 8.8 Hz), 7.75 (1H, s), 7.86 (1H, d, J = 1.4 Hz).

IR (KBr) 1669, 1499, 1435, 1341, 1273, 1248, 1144, 970, 824, 787 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>21</sub>H<sub>23</sub>NO<sub>5</sub>S (0.2H<sub>2</sub>O additive): C, 62.27; H, 5.82; N, 3.46. Found C, 62.17; H, 5.87; N, 3.45.  
10

#### Reference Example 74

In a mixture of THF and ethanol (1 : 1, v/v. 24.0ml ) was dissolved methyl 1-formyl-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate  
15 (501mg). To the solution was added 1N sodium hydroxide solution (15.0ml), and the mixture was stirred at room temperature for 16 hours. The mixture was a little concentrated, and to the residue was added 1N hydrochloric acid to convert weakly acidic solution. The  
20 mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give 1-formyl-7-  
25 (4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-

carboxylic acid (482mg) as white crystals.

mp 215 - 217°C.

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 1.03 (3H, t, J = 7.4 Hz), 1.71 - 1.84 (2H, m), 2.79 (2H, t, J = 5.4 Hz), 3.75 (2H, t, J = 5.6 Hz), 3.98 (2H, t, J = 6.5 Hz), 7.00 (2H, d, J = 8.8 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.59 - 7.65 (3H, m), 7.73 (1H, s), 7.82 (1H, d, J = 1.6 Hz), 8.53 (1H, s).

IR (KBr) 1701, 1682, 1644, 1501, 1366, 1294, 1256, 1233, 1186, 820 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>21</sub>H<sub>21</sub>NO<sub>4</sub>: C, 71.78; H, 6.02; N, 3.99. Found C, 72.08; H, 6.12; N, 4.06.

#### Reference Example 75

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 42.0ml) were dissolved 4-ethoxy-3-fluorophenyl borate (754mg) and methyl 7-bromo-1-(t-butoxycarbonyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1305mg). To the solution was added potassium carbonate (1132mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (158mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and

Ammon.  
B32

the residue was purified with silica gel column chromatography (75g, hexane : ethyl acetate = 4 : 1) to give methyl 1-(t-butoxycarbonyl)-7-(4-ethoxy-3-fluorophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate as yellow amorphous. The obtained methyl 1-(t-butoxycarbonyl)-7-(4-ethoxy-3-fluorophenyl)-2,3-dihydro-1-(t-butoxycarbonyl)-7-(4-ethoxy-3-fluorophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate was dissolved in ethyl acetate (80ml). To the solution was added 1N hydrochloric acid (15ml) at room temperature, and the mixture was stirred at 100°C for 1 hour and neutralized with 1N sodium hydroxide and saturated sodium hydrogen carbonate solution. To the mixture was added ethyl acetate, and the separated organic layer was washed with saturated sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (50g, hexane : ethyl acetate = 9 : 1 → 4 : 1 → 2 : 1) to give methyl 7-(4-ethoxy-3-fluorophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1007mg, 86%) as yellow crystals.

mp 134 - 137°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.47 (3H, t, J = 7.0 Hz), 2.89 (2H, t, J = 4.4 Hz), 3.41 (2H, q, J = 4.8 Hz), 3.81 (3H, s),

4.14 (2H, q,  $J = 7.1$  Hz), 4.63 (1H, brs), 6.67 (1H, d,  $J = 8.2$  Hz), 6.94 - 7.03 (1H, m), 7.19 - 7.31 (3H, m), 7.44 (1H, d,  $J = 2.2$  Hz), 7.71 (1H, s).

IR (KBr) 3385, 1696, 1624, 1503, 1478, 1435, 1312,  
5 1292, 1235, 1211, 1173  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{20}\text{H}_{20}\text{FNO}_3$ : C, 70.37; H, 5.91; N, 4.10.  
Found C, 70.35; H, 5.73; N, 4.03.

#### Reference Example 76

To anhydrous acetic acid (0.63ml) was added formic  
10 acid (0.31ml) at  $0^\circ\text{C}$ , and the mixture was stirred at  $60^\circ\text{C}$   
for 2 hours, cooled and diluted with THF (10ml). In THF  
(10ml) was dissolved methyl 7-(4-ethoxy-3-fluorophenyl)-  
2,3-dihydro-1H-1-benzazepine-4-carboxylate (510mg), and  
the solution was added dropwise to the previously  
15 prepared solution of formic anhydride in THF, at  $0^\circ\text{C}$ .  
The mixture was stirred at room temperature for 2 hours,  
and the solvent was evaporated under reduced pressure.  
The residue was diluted with ethyl acetate, washed with  
saturated sodium hydrogen carbonate solution, water and  
20 saturated brine, and dried with anhydrous magnesium  
sulfate. The solvent was evaporated under reduced  
pressure to give crystals, which were washed with ethyl  
acetate/hexane to give methyl 7-(4-ethoxy-3-fluorophenyl)-  
1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate  
25 (490mg, 89%) as white crystals.



mp 126 - 127.5°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.49 (3H, t, J = 7.0 Hz), 2.95 (2H, td, J = 5.5, 1.1 Hz), 3.83 - 3.88 (2H, m), 3.84 (3H, s), 4.17 (2H, q, J = 7.1 Hz), 7.05 (1H, t, J = 8.7 Hz), 7.19 (1H, d, J = 8.0 Hz), 7.28 - 7.37 (2H, m), 7.54 (1H, dd, J = 8.2, 2.2 Hz), 7.66 (1H, d, J = 2.2 Hz), 7.75 (1H, s), 8.54 (1H, s).

IR (KBr) 1707, 1674, 1501, 1269, 1236 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>21</sub>H<sub>20</sub>FNO<sub>4</sub>: C, 68.28; H, 5.46; N, 3.79.

10 Found C, 68.18; H, 5.52; N, 3.70.

#### Reference Example 77

In THF (10.0ml) was dissolved methyl 7-(4-ethoxy-3-fluorophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (345mg). To the solution was added pyridine (0.82ml), and to the mixture was added a solution of methanesulfonic anhydride (880mg) in THF (5.0ml), at room temperature. The mixture was stirred at room temperature for 37.5 hours, diluted with ethyl acetate, and washed with water, 1N hydrochloric acid, water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give methyl 7-(4-ethoxy-3-fluorophenyl)-1-methylsulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (193mg) as white crystals.

25

The mother liquor was concentrated, and the residue was purified with silica gel column chromatography (15g, hexane : ethyl acetate = 3 : 1) to give desired product. The obtained methyl 7-(4-ethoxy-3-fluorophenyl)-1-methylsulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate was collected and dissolved in a mixture of THF and ethanol (1 : 1, v/v, 10.0ml). To the solution was added 1N sodium hydroxide solution (3.6ml), and the mixture was stirred at room temperature for 16.5 hours. The mixture was a little concentrated, and to the residue was added 1N hydrochloric acid to convert weakly acidic solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give 7-(4-ethoxy-3-fluorophenyl)-1-methylsulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (213mg, 52%) as white crystals.

mp 237 - 239°C.

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 1.38 (3H, t, J = 7.0 Hz), 2.90 (2H, t, J = 5.4 Hz), 3.09 (3H, s), 3.70 (2H, t, J = 4.8 Hz), 4.16 (2H, q, J = 7.1 Hz), 7.23 (1H, d, J = 8.9 Hz), 7.50 - 7.56 (2H, m), 7.63 - 7.71 (2H, m), 7.76 (1H, s), 7.94 (1H, d, J = 1.6 Hz).

IR (KBr) 1686, 1669, 1622, 1499, 1350, 1271, 1150, 970, 801, 783  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{20}\text{H}_{20}\text{FNO}_5\text{S}$  ( $0.3\text{H}_2\text{O}$  additive): C, 58.47; H, 5.05; N, 3.41. Found C, 58.50; H, 4.94; N, 3.44.

5           Reference Example 78

          In a mixture of THF and ethanol (1 : 1, v/v, 20.0ml ) was dissolved methyl 7-(4-ethoxy-3-fluorophenyl)-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (441mg). To the solution was added 1N sodium  
10   hydroxide solution (12.0ml), and the mixture was stirred at room temperature for 16 hours. The mixture was a little concentrated, and to the residue was added 1N hydrochloric acid to convert weakly acidic solution. The mixture was extracted with ethyl acetate, and the organic  
15   layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give 7-(4-ethoxy-3-fluorophenyl)-1-formyl-2,3-dihydro-1H-1-  
20   benzazepine-4-carboxylic acid (435mg) as white crystals.  
mp 220 - 222°C.

$^1\text{H}$ -NMR (200 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.37 (3H, t,  $J = 7.0$  Hz), 2.74 (2H, t-like), 3.71 (2H, t-like), 4.16 (2H, q,  $J = 6.9$  Hz), 7.24 (1H, t,  $J = 8.8$  Hz), 7.41 (1H, d,  $J = 8.4$  Hz), 7.53 -  
25   7.58 (1H, m), 7.65 - 7.75 (3H, m), 7.99 (1H, d-like), 8.53

(1H, s).

IR (KBr) 1705, 1655, 1499, 1362, 1304, 1292, 1273, 1231, 1217, 1196, 1134, 816  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{20}\text{H}_{18}\text{FNO}_4$  ( $0.2\text{H}_2\text{O}$  additive): C, 66.92; H, 5.17; N, 3.90. Found C, 66.80; H, 5.28; N, 3.81.

#### Reference Example 79

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 36.0ml) were dissolved 4-[(2-methylthio)ethoxy]phenyl borate (760mg) and methyl 7-bromo-1-(t-butoxycarbonyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1141mg). To the solution was added potassium carbonate (990mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (138mg) and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (50g, hexane : ethyl acetate = 9 : 1  $\rightarrow$  4 : 1) to give methyl 1-(t-butoxycarbonyl)-7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1370mg, 98%) as white crystals.

mp 142.5 - 143.5°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.50 (9H, s), 2.24 (3H, s), 2.89 - 2.95 (4H, m), 3.63 - 3.70 (2H, br), 3.84 (3H, s), 4.21 (2H, t, J = 6.8 Hz), 6.99 (2H, d, J = 8.8 Hz), 7.46 - 7.58 (5H, m), 7.74 (1H, s).

IR (KBr) 1703, 1497, 1391, 1238, 1163 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>26</sub>H<sub>31</sub>NO<sub>5</sub>S: C, 66.50; H, 6.65; N, 2.98.

Found C, 66.27; H, 6.68; N, 3.04.

#### Reference Example 80

10 In ethyl acetate (80ml) was dissolved methyl 1-(t-butoxycarbonyl)-7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1320mg). To the solution was added 1N hydrochloric acid (15ml) at room temperature, and the mixture was stirred at 90°C for 1.5  
15 hours and neutralized with 1N sodium hydroxide and saturated sodium hydrogen carbonate solution. To the mixture was added ethyl acetate, and the separated organic layer was washed with saturated sodium hydrogen carbonate solution, water and saturated brine, and dried  
20 with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give methyl 7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (910mg) as yellow crystals.  
25 The mother liquor was concentrated under reduced pressure,

and the residue was purified with silica gel column chromatography (20g, hexane : ethyl acetate = 4 : 1) to give methyl 7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (910mg) as yellow crystals.

5 Yield, 1020mg (98%).

mp 114.5 - 117°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.24 (3H, s), 2.89 (2H, t, J = 4.2 Hz), 2.91 (2H, t, J = 6.8 Hz), 3.41 (2H, t, J = 4.7 Hz), 3.81 (3H, s), 4.20 (2H, t, J = 6.9 Hz), 4.63 - 4.72 (1H, br), 6.68 (1H, d, J = 8.4 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.32 (1H, dd, J = 8.2, 2.2 Hz), 7.46 (1H, d, J = 2.6 Hz), 7.47 (2H, d, J = 8.8 Hz), 7.73 (1H, s).

IR (KBr) 3380, 1698, 1609, 1499, 1269, 1244, 1209, 1174 cm<sup>-1</sup>.

15 Anal. Calcd. for C<sub>21</sub>H<sub>23</sub>NO<sub>3</sub>S: C, 68.27; H, 6.27; N, 3.79. Found C, 68.16; H, 6.22; N, 3.75.

#### Reference Example 81

To anhydrous acetic acid (0.65ml) was added formic acid (0.32ml) at 0°C, and the mixture was stirred at 55°C for 2 hours, air-cooled and diluted with THF (10ml). In THF (15ml) was dissolved methyl 7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (565mg), and the solution was added dropwise to the previously prepared solution of formic anhydride in THF, at 0°C. The mixture was stirred at room

temperature for 2 hours, and the solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate, washed with saturated sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give methyl 1-formyl-7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (578mg, 95%) as white crystals.  
mp 160 - 162°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.24 (3H, s), 2.93 (2H, t, J = 6.7 Hz), 2.95 (2H, t, J = 4.6 Hz), 3.83 - 3.88 (2H, m), 3.84 (3H, s), 4.22 (2H, t, J = 6.8 Hz), 6.97 - 7.04 (2H, m), 7.18 (1H, d, J = 8.2 Hz), 7.49 - 7.55 (2H, m), 7.56 (1H, dd, J = 8.2, 2.2 Hz), 7.68 (1H, d, J = 1.8 Hz), 7.76 (1H, s), 8.53 (1H, s).

IR (KBr) 1705, 1673, 1607, 1497, 1435, 1358, 1236, 1192, 824 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>22</sub>H<sub>23</sub>NO<sub>4</sub>S: C, 66.48; H, 5.83; N, 3.52.

Found C, 66.23; H, 5.93; N, 3.41.

#### Reference Example 82

In THF (10.0ml) were dissolved methyl 7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1-benzazepine-4-carboxylate (374mg) and pyridine (0.82ml). To the solution was added a solution of methanesulfonic

anhydride (882mg) in THF (5.0ml), at room temperature, and the mixture was stirred at 50°C for 13 hours. The mixture was diluted with ethyl acetate. and washed with water, 1N hydrochloric acid, water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (25g, hexane : ethyl acetate = 4 : 1 → 1 : 1) to give crystals, which were washed with ethyl acetate/hexane to give methyl 1-methylsulfonyl-7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (201mg, 44%) as white crystals. mp 157 - 159°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.24 (3H, s), 2.78 (3H, s), 2.92 (2H, t, J = 6.8 Hz), 3.05 (2H, td-like, J = 5.4 Hz (t)), 3.86 (3H, s), 3.87 (2H, t, J = 5.9 Hz), 4.22 (2H, t, J = 6.7 Hz), 7.00 (2H, d, J = 8.8 Hz), 7.49 - 7.57 (3H, m), 7.64 (1H, d, J = 2.0 Hz), 7.68 (1H, d, J = 8.4 Hz), 7.81 (1H, s).

IR (KBr) 1709, 1493, 1343, 1248, 1155 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>22</sub>H<sub>25</sub>NO<sub>5</sub>S<sub>2</sub>: C, 59.04; H, 5.63; N, 3.13.

Found C, 58.91; H, 5.65; N, 3.08.

#### Reference Example 83

In a mixture of THF and ethanol (1 : 1, v/v, 40.0ml) was dissolved methyl 1-formyl-7-[4-(2-



methythio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (531mg). To the solution was added 1N sodium hydroxide solution (13.5ml), and the mixture was stirred at room temperature for 14 hours. The mixture was a little concentrated, and to the residue was added 1N hydrochloric acid to convert weakly acidic solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give 1-formyl-7-[4-(2-methythio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (470mg, 92%) as white crystals.

mp 199 - 201°C.

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 2.18 (3H, s), 2.76 (2H, t-like), 2.87 (2H, t, J = 6.6 Hz), 3.72 (2H, t-like), 4.21 (2H, t, J = 6.2 Hz), 7.04 (2H, d, J = 8.8 Hz), 7.40 (1H, d, J = 8.8 Hz), 7.67 - 7.74 (4H, m), 7.91 (1H, s), 8.53 (1H, s).

IR (KBr) 1688, 1671, 1501, 1422, 1364, 1292, 1256, 1194, 1182, 1019, 822 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>21</sub>H<sub>21</sub>NO<sub>4</sub>S: C, 65.78; H, 5.52; N, 3.65. Found C, 65.49; H, 5.62; N, 3.58.

#### Reference Example 84

In a mixture of THF and ethanol (1 : 1, v/v, 20.0ml)

was dissolved methyl 1-methylsulfonyl-7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (169mg). To the solution was added 1N sodium hydroxide solution (5.5ml), and the mixture was stirred at room temperature for 14 hours. The mixture was a little concentrated, and to the residue was added 1N hydrochloric acid to convert weakly acidic solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give 1-methylsulfonyl-7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (157mg, 96%) as white crystals.

mp 234 - 239°C (dec.).

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 2.17 (3H, s), 2.87 (2H, t, J = 6.6 Hz), 2.90 (2H, t-like), 3.08 (3H, s), 3.70 (2H, t-like), 4.21 (2H, t, J = 6.6 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.51 (1H, d, J = 8.0 Hz), 7.61 - 7.75 (4H, m), 7.86 (1H, d-like).

IR (KBr) 1669, 1495, 1437, 1343, 1271, 1250, 1240, 1144, 824, 517 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>21</sub>H<sub>23</sub>NO<sub>3</sub>S<sub>2</sub>: C, 58.18; H, 5.35; N, 3.23.

Found C, 58.39; H, 5.39; N, 3.17.

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 42.0ml) were dissolved 4-(2-propoxy)ethoxyphenyl borate (920mg) and methyl 7-bromo-1-(t-butoxycarbonyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1308mg). To the solution was added potassium carbonate (1135mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (119mg), and the mixture was heated to reflux under argon atmosphere for 14.5 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. and the residue was purified with silica gel column chromatography (50g, hexane : ethyl acetate = 9 : 1 → 3 : 1) to give methyl 1-(t-butoxycarbonyl)-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1536mg, 93%) as colorless oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J = 7.4 Hz), 1.49 (9H, s), 1.66 (2H, sextet, J = 7.1 Hz), 2.91 (2H, t, J = 4.7 Hz), 3.52 (2H, t, J = 6.7 Hz), 3.55 - 3.82 (2H, br), 3.82 (2H, t, J = 4.9 Hz), 3.83 (3H, s), 4.18 (2H, t, J = 4.9 Hz), 7.01 (2H, d, J = 8.8 Hz), 7.45 - 7.58 (5H, m), 7.74 (1H, s).

IR (KBr) 1705, 1497, 1391, 1287, 1236, 1163, 1086 cm<sup>-1</sup>.

In ethyl acetate (80ml) was dissolved methyl 1-(t-butoxycarbonyl)-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1536mg). To the solution was added 1N hydrochloric acid (20ml) at room temperature, and the mixture was stirred at 90°C for 1 hour and neutralized with saturated sodium hydrogen carbonate solution, and to the mixture was added ethyl acetate. The separated organic layer was washed with saturated sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give methyl 7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (523mg) as yellow crystals. The mother liquor was concentrated under reduced pressure, and the residue was purified with silica gel column chromatography (65g, hexane : ethyl acetate = 3 : 1) to give methyl 7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (606mg) as yellow crystals. Yield, 1129mg (93%).

mp 86 - 88°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.4 Hz), 1.65 (2H, sextet, J = 7.2 Hz), 2.89 (2H, t, J = 4.5 Hz), 3.40 (2H, brs), 3.51 (2H, t, J = 6.8 Hz), 3.81 (3H, s and 2H, t, J =

4.9 Hz), 4.16 (2H, t, J = 5.0 Hz), 4.60 (1H, brs), 6.67 (1H, d, J = 8.4 Hz), 6.95 - 7.01 (2H, m), 7.32 (1H, dd, J = 8.2, 2.2 Hz), 7.42 - 7.48 (2H, m), 7.46 (1H, d, J = 2.0 Hz), 7.73 (1H, s).

5 IR (KBr) 3380, 1698, 1611, 1501, 1269, 1246, 1209, 1177, 820  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{23}\text{H}_{27}\text{NO}_4$ : C, 72.42; H, 7.13; N, 3.67. Found C, 72.28; H, 7.09; N, 3.73.

#### Reference Example 87

10 To anhydrous acetic acid (0.51ml) was added formic acid, (0.25ml) at 0°C, and the mixture was stirred at 55°C for 2 hours, air-cooled and diluted with THF (10ml). In THF (15ml) was dissolved methyl 7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-  
15 carboxylate (462mg), and the solution was added dropwise to the previously prepared solution of formic anhydride in THF, at 0°C. The mixture was stirred at room temperature for 2 hours, and the solvent was evaporated under reduced pressure. The residue was diluted with  
20 ethyl acetate, washed with saturated sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous, magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give methyl 1-  
25 formyl-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-

benzazepine-4-carboxylate (496mg) as white crystals.

mp 107 - 108°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J = 7.3 Hz), 1.62 (2H, sextet, J = 7.2 Hz), 2.95 (2H, t, J = 4.7 Hz), 3.52 (2H, t, J = 6.7 Hz), 3.80 - 3.88 (4H, m), 3.84 (3H, s), 4.18 (2H, t, J = 4.9 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.17 (1H, d, J = 8.0 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.56 (1H, dd, J = 8.0, 2.2 Hz), 7.68 (1H, d, J = 1.8 Hz), 7.75 (1H, s), 8.53 (1H, s).

IR (KBr) 1709, 1678, 1360, 1291, 1236, 1192, 824 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>24</sub>H<sub>27</sub>NO<sub>3</sub>: C, 70.40; H, 6.65; N, 3.42. Found C, 70.37; H, 6.64; N, 3.41.

#### Reference Example 88

In THF (20.0ml) were dissolved methyl 7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (600mg) and pyridine (1.53ml). To the solution was added a solution of methanesulfonic anhydride (1.64g) in THF (10.0ml), at room temperature, and the mixture was stirred at 50°C for 14.5 hours. The mixture was diluted with ethyl acetate, and washed with water, 1N hydrochloric acid, water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (35g, hexane : ethyl acetate = 4 : 1 → 2:1) to give crystals, which were washed with ethyl

- acetate/hexane to give methyl 1-methylsulfonyl-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (231mg) as white crystals. The mother liquor was concentrated under reduced pressure, and the residue
- 5 was purified with silica gel column chromatography (350g, hexane : ethyl acetate = 3 : 1 → 2 : 1) to give methyl 1-methylsulfonyl-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (170mg) as white crystals.
- 10 Yield, 402mg (56%).
- mp 119 - 121°C.
- <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J = 7.4 Hz), 1.65 (2H, sextet, J = 7.3 Hz), 2.78 (3H, s), 3.05 (2H, t, J = 5.5 Hz), 3.52 (2H, t, J = 6.8 Hz), 3.80 - 3.89 (4H, m), 3.85 (3H, s),
- 15 4.18 (2H, t, J = 5.0 Hz), 7.02 (2H, d, J = 8.8 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.54 (1H, dd, J = 8.4, 2.2 Hz), 7.63 (1H, d, J = 1.8 Hz), 7.67 (1H, d, J = 8.4 Hz), 7.80 (1H, s).
- IR (KBr) 1709, 1493, 1345, 1289, 1248, 1188, 1155, 1132, 1103 cm<sup>-1</sup>.
- 20 Anal. Calcd. for C<sub>24</sub>H<sub>29</sub>NO<sub>6</sub>S (0.4H<sub>2</sub>O additive): C, 61.76; H, 6.44; N, 3.00. Found C, 61.61; H, 6.22; N, 2.96.

#### Reference Example 89

- In a mixture of THF and ethanol (1 : 1, v/v, 30.0ml) was dissolved methyl 1-formyl-7-[4-(2-
- 25 propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-

carboxylate (445mg). To the solution was added 1N sodium hydroxide solution (11.0ml), and the mixture was stirred at room temperature for 13 hours. The mixture was a little concentrated, and to the residue was added 1N hydrochloric acid to convert weakly acidic solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give 1-formyl-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (430mg) as white crystals.

mp 165 - 166°C.

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 0.88 (3H, t, J = 7.5 Hz), 1.54 (2H, sextet, J = 7.1 Hz), 2.75 (2H, t-like), 3.43 (2H, t, J = 6.8 Hz), 3.72 (4H, t, J = 4.6 Hz), 4.15 (2H, t, J = 4.6 Hz), 7.04 (2H, d, J = 8.8 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.69 (2H, d, J = 8.8 Hz), 7.67 - 7.74 (2H, m), 7.92 (1H, d, J = 1.8 Hz), 8.53 (1H, s).

IR (KBr) 1682, 1499, 1360, 1291, 1258, 1246, 1192, 1130, 820 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>23</sub>H<sub>25</sub>NO<sub>5</sub>: C, 69.86; H, 6.37; N, 3.54. Found C, 69.69; H, 6.38; N, 4.59.

#### Reference Example 90

In a mixture of THF and ethanol (1 : 1, v/v, 30.0ml)



was dissolved methyl 1-methylsulfonyl-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (354mg). To the solution was added 1N sodium hydroxide solution (7.7ml), and the mixture was stirred  
5 at room temperature for 15.5 hours. The mixture was a little concentrated, and to the residue was added 1N hydrochloric acid to convert weakly acidic solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine, and  
10 dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give 1-methylsulfonyl-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (337mg, 98%) as white  
15 crystals.

mp 213 - 215°C.

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 0.88 (3H, t, J = 7.3 Hz), 1.54 (2H, sextet, J = 7.0 Hz), 2.50 (3H, s), 3.33 (2H, t-like), 3.43 (2H, t, J = 6.6 Hz), 3.72 (4H, t-like), 4.15 (2H, t-  
20 like), 7.04 (2H, d, J = 8.8 Hz), 7.51 (1H, d, J = 8.0 Hz), 7.63 - 7.75 (4H, m), 7.88 (1H, s).

IR (KBr) 1669, 1493, 1341, 1294, 1271, 1250, 1154, 1128, 785, 519 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>23</sub>H<sub>27</sub>NO<sub>6</sub>S (0.1H<sub>2</sub>O additive): C, 61.75; H, 6.13; N, 3.13. Found C, 61.50; H, 5.88; N, 3.01.  
25

## Reference Example 91

In THF (1000ml) was dissolved 4-[[N-(benzyloxy)carbonyl]amino]butyric acid (50.0g). To the solution were added propyl bromide (77.5g) and sodium iodide (94.4g), and to the mixture was gradually added at  
5 -5°C 60% sodium hydride (25.2g). Under nitrogen atmosphere, the mixture was stirred at 0°C for 15 minutes and then at 75°C for 4 days. The mixture was concentrated under reduced pressure, and to the residue  
10 was added water. The aqueous layer was adjusted to pH11 with sodium hydroxide (granule) and washed with ether (twice). The aqueous layer was adjusted to pH2 with concentrated hydrochloric acid and washed with ethyl acetate (thrice). The organic layer was washed with 1M  
15 sodium thiosulfate solution and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give 4-[[N-(benzyloxy)carbonyl]-N-propylamino]butyric acid (35.8g, 61%).  
20 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.88 (3H, t, J = 7.3 Hz), 1.50 - 1.57 (2H, m), 1.85 - 1.90 (2H, m), 2.34 - 2.41 (2H, m), 3.17 - 3.30 (4H, m), 5.13 (2H, s), 7.35 (5H, s).

## Reference Example 92

To 4-[[N-(benzyloxy)carbonyl]-N-propylamino]butyric  
25 acid (35.8g) was added t-butanol (350ml), and then was

added di-*t*-butyl dicarbonate (140g). To the mixture was added dimethylaminopyridine (4.69g), and the mixture was stirred at room temperature for 30 minutes. The mixture was concentrated under reduced pressure, and the residue was purified with silica gel column chromatography to give pale yellow oil of *t*-butyl 4-[[N-(benzyloxy)carbonyl]-N-propylamino]butyrate (23.8g, 55%).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.88 (3H, t, J = 7.3 Hz), 1.45 (9H, s), 1.52 - 1.59 (2H, m), 1.81 - 1.84 (2H, m), 2.23 (2H, t, J = 7.1 Hz), 3.17 - 3.27 (4H, m), 5.13 (2H, s), 7.35 (5H, s).

IR (KBr) 2969, 1728, 1703, 1476, 1456, 1422, 1368, 1242, 1155, 1136 cm<sup>-1</sup>.

#### Reference Example 93

In methanol (250ml) was dissolved *t*-butyl 4-[[N-(benzyloxy) carbonyl]-N-propylamino] butyrate (23.7g), and to the solution was added 10% palladium on carbon (2.37g). The mixture was stirred under hydrogen atmosphere at room temperature for 2 hours, and 10% palladium on carbon was removed. The solvent was evaporated under reduced pressure to give colorless oil of *t*-butyl 4-propylaminobutyrate [16.8g (containing methanol)].

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.92 (3H, t, J = 7.1 Hz), 1.45 (9H, s), 1.47 - 1.67 (4H, m), 1.70 - 1.85 (2H, m), 2.25 (2H, q,

J = 7.9 Hz), 2.60 (2H, dt, J = 11.6, 7.2 Hz), 3.21 (1H, m).  
IR (KBr) 2967, 2936, 1728, 1480, 1456, 1424, 1368, 1246,  
1155  $\text{cm}^{-1}$ .

#### Reference Example 94

5 To a solution of t-butyl 4-propylaminobutyrate  
(14.2g, 70.7mmol) in DMF (20ml) were added 5-bromo-2-  
fluorobenzaldehyde (14.4g, 70.9mmol) and potassium  
carbonate (14.7g, 106mmol) at room temperature, and the  
mixture was stirred at 80°C for 94 hours. The mixture  
10 was diluted with ethyl acetate, washed with water and  
saturated brine, and dried with anhydrous magnesium  
sulfate. The solvent was evaporated under reduced  
pressure, and the residue was purified with silica gel  
column chromatography (hexane : ethyl acetate = 10 : 1)  
15 to give yellow oil of t-butyl 4-(4-bromo-2-  
formylphenyl)propylaminobutyrate (14.2g, 52%).  
 $^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.84 (3H, t, J = 7.8 Hz), 1.45 (9H,  
s), 1.42 - 1.63 (2H, m), 1.81 (2H, quint, J = 7.4 Hz), 2.19  
(2H, t, J = 7.5 Hz), 3.09 (2H, t, J = 7.6 Hz), 3.17 (2H, t,  
20 J = 7.5 Hz), 7.06 (1H, d, J = 8.8 Hz), 7.56 (1H, dd, J =  
8.7, 2.5 Hz), 7.90 (1H, d, J = 2.6 Hz), 10.24 (1H, s).  
IR (KBr) 2971, 1730, 1694, 1480, 1368, 1244, 1157  $\text{cm}^{-1}$ .

#### Reference Example 95

In a mixture of t-butanol and toluene (1:10, v/v,  
25 440ml) was dissolved t-butyl 4-(4-bromo-2-

formylphenyl)propylbutyrate (14.1g). To the solution was added sodium t-butoxide (5.29g) at room temperature, and the mixture was heated to reflux for 1 hour (90°C), air-cooled, diluted with ethyl acetate, washed with water, 0.5N sodium hydroxide solution, water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give yellow oil of t-butyl 7-bromo-1-propyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (8.07g, 60%).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J = 7.5 Hz), 1.53 (9H, s), 1.68 (2H, sextet, J = 7.6 Hz), 2.75 (2H, t, J = 4.4 Hz), 3.18 - 3.26 (4H, m), 6.67 (1H, d, J = 9.2 Hz), 7.22 (1H, dd, J = 8.8, 2.6 Hz), 7.39 (1H, d, J = 2.6 Hz), 7.46 (1H, s).

IR (KBr) 2969, 1698, 1497, 1368, 1269, 1254, 1159 cm<sup>-1</sup>.

#### Reference Example 96

In ethyl acetate (80ml) was dissolved t-butyl 7-bromo-1-propyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (8.05g). To the solution was added a solution of 4N hydrochloric acid in ethyl acetate (80ml), and the mixture was stirred at room temperature for 12 hours. To the mixture was added water, and the mixture was adjusted to pH2 with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was

dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue of solid was washed with hexane-ethyl acetate to give yellow crystals of 7-bromo-1-propyl-2,3-dihydro-1H-1-

5 benzazepine-4-carboxylic acid (2.61g, 39%).

mp 172 - 173°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J = 7.3 Hz), 1.70 (2H, sextet, J = 7.5 Hz), 2.81 (2H, t, J = 4.6 Hz), 3.22 - 3.29 (4H, m), 6.70 (1H, d, J = 8.8 Hz), 7.25 (1H, dd, J = 8.8, 10 2.6 Hz), 7.43 (1H, d, J = 2.0 Hz), 7.69 (1H, s).

IR (KBr) 2963, 1674, 1497, 1410, 1277, 1171 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>14</sub>H<sub>16</sub>BrNO<sub>2</sub>: C, 54.21; H, 5.20; N, 4.52.

Found C, 54.17; H, 5.05; N, 4.42.

#### Reference Example 97

15 In DMF (12ml) was dissolved 7-bromo-1-propyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (2430mg, 7.83mmol). To the solution was added thionyl chloride (1.4ml), and the mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced  
20 pressure, and the residue was suspended in THF (50ml). To 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (2757mg) was added THF (40ml), and to the mixture was added dropwise triethylamine (8.2ml). The mixture was stirred at room  
25 temperature for 30 minutes, and to the mixture was added

dropwise the previously prepared acid chloride suspension in THF, at 0°C. The mixture was stirred at room temperature for 21 hours, and the mixture was concentrated. To the mixture was added ethyl acetate,

5 and the mixture was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (ethyl acetate → ethyl acetate:ethanol=10:1) and recrystallized from ethyl acetate-hexane to give yellow crystals of 7-bromo-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1-propyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (3219mg, 80%).

mp 134 - 136°C.

15 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.97 (3H, t, J = 7.5 Hz), 1.60 - 1.80 (6H, m), 2.21 (3H, s), 2.57 - 2.70 (1H, m), 2.89 (2H, t, J = 4.6 Hz), 3.22 - 3.30 (4H, m), 3.37 (2H, td, J = 11.1, 2.8 Hz), 3.57 (2H, s), 4.01 - 4.07 (2H, m), 6.71 (1H, d, J = 9.2 Hz), 7.19 (1H, s), 7.24 (1H, dd, J = 9.0, 2.6 Hz),  
20 7.30 (2H, d, J = 8.4 Hz), 7.41 (1H, d, J = 2.6 Hz), 7.50 (1H, s), 7.52 (2H, d, J = 8.4 Hz).

IR (KBr) 2957, 1645, 1597, 1514, 1497, 1406, 1314, 1246, 1173 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>27</sub>H<sub>34</sub>BrN<sub>3</sub>O<sub>2</sub>: C, 63.28; H, 6.69; N, 8.20.

25 Found C, 63.19; H, 6.54; N, 8.05.

Amen.  
B33

Working Example 1 (Production of Compound 1)

In DMF (10ml) was dissolved 7-[4-(2-ethoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.18g). To the solution was added, under ice-cooling, thionyl chloride (0.09ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.12g) and triethylamine (0.33ml) in THF (10ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 7-[4-(2-ethoxyethoxy)phenyl]-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxaldehyde (Compound 1) (0.23g) as colorless crystals. mp 192 - 194°C.



<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.26 (3H, t, J = 7.0 Hz), 1.59 - 1.75 (4H, m), 2.21 (3H, s), 2.59 - 2.70 (1H, m), 3.02 (2H, t, J = 5.1 Hz), 3.37 (2H, dt, J = 1.5, 11.4 Hz), 3.57 (2H, s), 3.63 (2H, q, J = 7.0 Hz), 3.83 (2H, t, J = 4.8 Hz), 3.91 (2H, t, J = 5.1 Hz), 4.01 - 4.07 (2H, m), 4.18 (2H, t, J = 4.8 Hz), 7.02 (2H, d, J = 8.8 Hz), 7.18 (1H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.45 - 7.57 (6H, m), 7.65 (1H, br), 7.66 (1H, d, J = 1.8 Hz), 8.54 (1H, s).

IR (KBr) ν: 3297, 2946, 2847, 1669 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>35</sub>H<sub>41</sub>N<sub>3</sub>O<sub>5</sub>: C, 72.02; H, 7.08; N, 7.20.  
Found C, 71.90; H, 6.79; N, 7.05.

#### Working Example 2 (Production of Compound 2)

In DMF (5ml) was dissolved 7-[4-(3-ethoxypropoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.25g). To the solution was added, under ice-cooling, thionyl chloride (0.12ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and the residue was suspended in THF (15ml). The suspension was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.16g) and triethylamine (0.44ml) in THF (5ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was

added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 7-[4-(3-ethoxypropoxy)phenyl]-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 2) (0.29g) as colorless crystals.

mp 166 - 169°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.22 (3H, t, J = 7.0 Hz), 1.64 - 1.82 (4H, m), 2.02 - 2.15 (2H, m), 2.21 (3H, s), 2.60 - 2.68 (1H, m), 3.03 (2H, t, J = 5.5 Hz), 3.37 (2H, dt, J = 2.6, 11.2 Hz), 3.46 - 3.66 (6H, m), 3.92 (2H, t, J = 5.5 Hz), 4.02 - 4.07 (2H, m), 4.13 (2H, t, J = 6.3 Hz), 7.01 (2H, d, J = 8.8 Hz), 7.19 (1H, d, J = 8.2 Hz), 7.32 (2H, d, J = 8.6 Hz), 7.47 - 7.60 (6H, m), 7.68 (1H, d, J = 2.0 Hz), 8.55 (1H, s).

IR (KBr) ν: 2946, 2849, 1669 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>36</sub>H<sub>43</sub>N<sub>3</sub>O<sub>5</sub>: C, 72.34; H, 7.25; N, 7.03.

Found C, 72.54; H, 7.11; N, 7.00.

#### Working Example 3 (Production of Compound 3)

In DMF (5ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.23g). To the solution was added, under ice-cooling, thionyl chloride (0.11ml),

[illegible]

20  $^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.94 (3H, t,  $J = 7.2$  Hz), 1.31 - 1.49  
(2H, m), 1.55 - 1.65 (2H, m), 1.70 - 1.75 (4H, m), 2.21 (3H,  
s), 2.60 - 2.71 (1H, m), 3.04 (2H, t,  $J = 5.5$  Hz), 3.37 (2H,  
dt,  $J = 3.2, 11.3$  Hz), 3.53 - 3.59 (4H, m), 3.82 (2H, t,  $J$   
= 4.9 Hz), 3.92 (2H, t,  $J = 5.5$  Hz), 4.01 - 4.07 (2H, m),  
25 4.18 (2H, t,  $J = 4.9$  Hz), 7.03 (2H, d,  $J = 8.8$  Hz), 7.19

(1H, d,  $J = 8.2$  Hz), 7.32 (2H, d,  $J = 8.4$  Hz), 7.46 - 7.56 (6H, m), 7.68 (1H, d,  $J = 1.8$  Hz), 8.55 (1H, s).

IR (KBr)  $\nu$ : 2940, 1669, 1518, 1497  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{37}\text{H}_{45}\text{N}_3\text{O}_5$ : C, 72.64; H, 7.41; N, 6.87.

5 Found C, 72.48; H, 7.11; N, 6.71.

Working Example 4 (Production of Compound 4)

In DMF (3.5ml) was dissolved 7-[4-[N-(2-ethoxyethyl)-N-methylamino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.17g). To the  
10 solution was added, under ice-cooling, thionyl chloride (0.08ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (25ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline  
15 (0.11g) and triethylamine (0.31ml) in THF (6.5ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature for 1 hour, poured into water and extracted with ethyl acetate. The organic  
20 layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column chromatography (ethyl acetate/ethanol) to give crude crystals, which were recrystallized from ethanol to  
25 give 7-[4-[N-(2-ethoxyethyl)-N-methylamino]phenyl]-1-

formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 4) (0.14g) as pale yellow crystals. mp 157 - 158°C.

- 5 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.21 (3H, t, J = 7.4 Hz), 1.59 - 1.82 (4H, m), 2.20 (3H, s), 2.64 (1H, m), 2.96 - 3.06 (2H, m), 3.05 (3H, s), 3.30 - 3.43 (2H, m), 3.52 (2H, q, J = 7.0 Hz), 3.57 (2H, s), 3.56 - 3.63 (2H, m), 3.88 - 3.94 (2H, m), 3.99 - 4.07 (2H, m), 6.80 (2H, d, J = 8.8 Hz), 7.16 (1H, m), 10 7.29 - 7.56 (7H, m), 7.66 (1H, s), 8.53 (1H, s).  
IR (KBr) v: 2946, 2849, 1669, 1609, 1505, 1360, 1316, 1204, 1113, 814 cm<sup>-1</sup>.

#### Working Example 5 (Production of Compound 5)

- In DMF (5ml) was dissolved 7-[4-[N-(2-ethoxyethyl)-  
15 N-ethylamino]phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.2g). To the solution was added, under ice-cooling, thionyl chloride (0.09ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was  
20 evaporated, and the residue was dissolved in THF (25ml). The solution was added dropwise a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.20g) and triethylamine (0.35ml) in THF (5ml), under ice-cooling, and the mixture was stirred under nitrogen  
25 atmosphere stirred at room temperature overnight. Under

reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous

5 magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 7-[4-[N-(2-ethoxyethyl)-N-ethylamino]phenyl]-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-

10 dihydro-1H-1-benzazepine-4-carboxamide (Compound 5) (0.23g) as pale yellow crystals.

mp 162 - 164°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.17 - 1.30 (6H, m), 1.70 - 1.80 (4H, m), 2.21 (3H, s), 2.55 - 2.75 (1H, m), 3.03 (2H, t, J = 5.2

15 Hz), 3.33 - 3.62 (12H, m), 3.92 (2H, t, J = 5.2 Hz), 4.01 - 4.14 (2H, m), 6.78 (2H, d, J = 8.8 Hz), 7.16 (1H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.45 - 7.56 (6H, m), 7.66 (1H, d, J = 2.0 Hz), 8.54 (1H, s).

IR (KBr) ν: 2849, 1661, 1609, 1552, 1501 cm<sup>-1</sup>.

20 Anal. Calcd. for C<sub>37</sub>H<sub>46</sub>N<sub>4</sub>O<sub>4</sub>·0.2H<sub>2</sub>O: C, 72.33; H, 7.61; N, 9.12. Found C, 72.30; H, 7.70; N, 9.23.

#### Working Example 6 (Production of Compound 6)

In DMF (7ml) was dissolved 7-[4-[N-ethyl-N-(2-propoxyethyl)amino]phenyl]-1-formyl-2,3-dihydro-1H-1-

25 benzazepine-4-carboxylic acid (0.25g). To the solution

was added, under ice-cooling, thionyl chloride (0.11ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (25ml).

5 The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.16g) and triethylamine (0.41ml) in THF (5ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced  
10 pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude  
15 crystals, which were recrystallized from ethyl acetate/hexane to give 7-[4-[N-ethyl-N-(2-propoxyethyl)amino]phenyl]-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 6)  
20 (0.27g) as pale yellow crystals.  
mp 146 - 149°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.20 (3H, t, J = 6.9 Hz), 1.59 - 1.75 (6H, m), 2.21 (3H, s), 2.55 - 2.75 (1H, m), 3.03 (2H, t, J = 5.4 Hz), 3.31 - 3.61 (12H, m),  
25 3.92 (2H, t, J = 5.4 Hz), 4.01 - 4.14 (2H, m), 6.78 (2H, d,

$J = 9.2$  Hz), 7.16 (1H, d,  $J = 8.4$  Hz), 7.32 (2H, d,  $J = 8.4$  Hz), 7.45 - 7.56 (6H, m), 7.66 (1H, d,  $J = 2.2$  Hz), 8.54 (1H, s).

IR (KBr)  $\nu$ : 2942, 1669  $\text{cm}^{-1}$ .

- 5    Anal. Calcd. for  $\text{C}_{39}\text{H}_{48}\text{N}_4\text{O}_4 \cdot 0.3\text{H}_2\text{O}$ : C, 72.42; H, 7.77; N, 8.89.  
Found C, 72.57; H, 7.53; N, 8.59.

Working Example 7 (Production of Compound 7)

In THF (15ml) was suspended 7-[4-(2-ethoxyethoxy)phenyl]-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.14g). To the suspension were added, under ice-cooling, thionyl chloride (0.04ml) and DMF (catalytic amount), and the mixture was stirred at room temperature for 1.5 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (15ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.08g) and triethylamine (0.14ml) in THF (15ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature for 1 hour. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-[4-(2-ethoxyethoxy)phenyl]-1-



methanesulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 7) (0.15g) as colorless amorphous.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.26 (3H, t, J = 7.0 Hz), 1.60 - 1.76  
 5 (4H, m), 2.22 (3H, s), 2.67 (1H, br), 2.89 (3H, s), 3.14  
 (2H, t, J = 5.2 Hz), 3.37 (2H, dt, J = 3.0, 11.0 Hz), 3.59  
 (2H, s), 3.63 (2H, q, J = 7.0 Hz), 3.83 (2H, t, J = 4.8 Hz),  
 3.92 (2H, t, J = 5.2 Hz), 4.01 - 4.07 (2H, m), 4.18 (2H, t,  
 J = 4.6 Hz), 7.02 (2H, d, J = 8.8 Hz), 7.33 (2H, d, J = 8.8  
 10 Hz), 7.49 - 7.67 (8H, m).

IR (KBr) ν: 2934, 2849, 1661, 1609, 1520, 1495 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>35</sub>H<sub>43</sub>N<sub>3</sub>O<sub>6</sub>S: C, 66.33; H, 6.84; N, 6.63.

Found C, 66.39; H, 6.76; N, 6.57.

~~Working Example 8 (Production of Compound 8)~~

*Ames B36*  
 15 In THF (5ml) was dissolved 7-[4-(3-ethoxypropoxy)phenyl]-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.20g). To the solution were added, under ice-cooling, thionyl chloride (0.06ml) and DMF (catalytic amount), and the mixture was stirred  
 20 at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated, and the residua was dissolved in THF (15ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.11g) and triethylamine (0.19ml)  
 25 in THF (5ml), under ice-cooling, and the mixture was

stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 7-[4-(3-ethoxypropoxy)phenyl]-1-methanesulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 8) (0.22g) as colorless crystals.

mp 157 - 160°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 1.22 (3H, t, J = 7.0 Hz), 1.65 - 1.76 (4H, m), 2.06 - 2.15 (2H, m), 2.22 (3H, s), 2.55 - 2.78 (1H, m), 2.89 (3H, s), 3.14 (2H, t, J = 5.1 Hz), 3.38 (2H, dt, J = 2.6, 11.2 Hz), 3.46 - 3.65 (6H, m), 3.92 (2H, t, J = 5.1 Hz), 3.95 - 4.15 (4H, m), 7.00 (2H, d, J = 9.2 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.49 - 7.67 (9H, m).

IR (KBr) v: 2926, 2851, 1671, 1595, 1524 cm<sup>-1</sup>.

#### Working Example 9 (Production of Compound 9)

In a mixture of water:ethanol:toluene (1:1: 10, v/v, 18.0ml) were dissolved 4-(2-ethoxyethoxy)phenyl borate (315mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-

1001334-141501

dihydro-1H-1-benzazepine-4-carboxamide (485mg). To the solution was added potassium carbonate (332mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added

5 tetrakis(triphenylphosphine)palladium (46mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate.

10 The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (30g, ethyl acetate : ethanol = 9 : 1) and recrystallized from ethanol to give 7-[4-(2-ethoxyethoxy)phenyl]-1-methyl-N-[4-[[N-methyl-N-

15 (tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 9) (230mg, 40%) as yellow crystals.

mp 122 - 125°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t, J = 7.0 Hz), 1.23 - 1.76 (4H, m), 2.20 (3H, s), 2.53 - 2.71 (1H, m), 2.94 (2H, t, J = 4.4 Hz), 3.07 (3H, s), 3.32 (2H, t, J = 4.5 Hz), 3.37 (2H, td, J = 11.4, 2.9 Hz), 3.56 (2H, s), 3.62 (2H, q, J = 7.0 Hz), 3.81 (2H, t, J = 4.9 Hz), 4.01 - 4.07 (2H, m), 4.16 (2H, t, J = 5.0 Hz), 6.86 (1H, d, J = 8.6 Hz), 6.97

25 (2H, d, J = 8.8 Hz), 7.29 (2H, d, J = 9.0 Hz), 7.38 (1H, s),

7.43 (1H, dd,  $J = 8.6, 2.2$  Hz), 7.47 (2H, d,  $J = 8.8$  Hz), 1 H (d) was concealed under 7.49, 7.54 (2H, d,  $J = 8.6$  Hz), 7.66 (1H, s).

IR (KBr) 2946, 2847, 1653, 1607, 1501, 1312, 1244, 1186,  
5 1119, 814  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{35}\text{H}_{43}\text{N}_3\text{O}_4$ : C, 73.78; H, 7.61; N, 7.38.  
Found C, 73.93; H, 7.39; N, 7.44.

Working Example 10 (Production of Compound 10)

10 In DMF (5.0ml) was dissolved 1-methylsulfonyl-7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (207mg). To the solution was added thionyl chloride (0.09ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and to the residue was added  
15 THF (10.0ml). On the other hand, to 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (168mg) was added THF (5.0ml), and then was added triethylamine (0.50ml). To the obtained mixture was added dropwise at 0°C the previously prepared  
20 acid chloride suspension, and the mixture was stirred at room temperature for 4 hours. To the mixture was added ethyl acetate, and the mixture was washed with water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated  
25 under reduced pressure, and the residue was purified with

silica gel column chromatography (15g, ethyl acetate → ethyl acetate : ethanol : triethylamine = 100 : 10 : 1) and recrystallized from ethanol to give 1-methylsulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 10) (176mg, 58%) as white crystals.

mp 174 - 177°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.64 - 1.77 (4H, m), 2.21 (3H, s), 2.24 (3H, s), 2.60 - 2.72 (1H, m), 2.89 (3H, s), 2.92 (2H, t, J = 6.9 Hz), 3.14 (2H, t, J = 5.3 Hz), 3.38 (2H, td, J = 11.4, 2.9 Hz), 3.58 (2H, s), 3.92 (2H, t, J = 5.3 Hz), 4.02 - 4.07 (2H, m), 4.22 (2H, t, J = 6.8 Hz), 7.00 (2H, d, J = 8.8 Hz), 7.33 (2H, d, J = 8.4 Hz), 7.50 - 7.67 (9H, m).  
IR (KBr) 1655, 1607, 1517, 1493, 1341, 1314, 1248, 1154cm<sup>-1</sup>.  
Anal. Calcd. for C<sub>34</sub>H<sub>41</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub>: C, 64.22; H, 6.50; N, 6.61. Found C, 64.03; H, 6.51; N, 6.55.

Working Example 11 (Production of Compound 11)

In DMF (10.0ml) was dissolved 1-formyl-7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (484mg). To the solution was added thionyl chloride (0.23ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and to the residue was added THF (10.0ml). On the other hand, to 4-[[N-methyl-N-

(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (444mg) was added THF (10.0ml), and then was added triethylamine (1.32ml). To the obtained mixture was added dropwise at 0°C the previously prepared acid chloride suspension, and the mixture was stirred at room temperature for 3 hours. To the mixture was added ethyl acetate and the mixture was washed with water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (30g, ethyl acetate → ethyl acetate : ethanol : triethylamine = 100 : 10 : 1) and recrystallized from ethanol to give 1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(2-methylthio)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 11) (555mg, 75%) as white crystals.

mp 180 - 183°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.64 - 1.77 (4H, m), 2.21 (3H, s), 2.24 (3H, s), 2.59 - 2.67 (1H, m), 2.92 (2H, t, J = 6.8 Hz), 3.04 (2H, t, J = 4.6 Hz), 3.37 (2H, td, J = 11.2, 2.9 Hz), 3.57 (2H, s), 3.92 (2H, t, J = 5.3 Hz), 4.01 - 4.07 (2H, m), 4.22 (2H, t, J = 6.8 Hz), 7.01 (2H, d, J = 8.8 Hz), 7.20 (1H, d, J = 8.0 Hz), 7.32 (2H, d, J = 8.8 Hz), 7.47 - 7.58 (7H, m), 7.68 (1H, d, J = 1.8 Hz), 8.55 (1H, s).

IR (KBr) 1667, 1607, 1514, 1497, 1360, 1314, 1246, 824  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{34}\text{H}_{39}\text{N}_3\text{O}_4\text{S}$  ( $0.2\text{H}_2\text{O}$  additive): C, 69.29; H, 6.74; N, 7.13. Found C, 69.09; H, 6.58; N, 7.01.

Working Example 12 (Production of Compound 12)

5 In a mixture of water : ethanol : toluene (1 : 1 :  
10, v/v, 18.0ml) were dissolved 4-(2-propoxyethoxy)phenyl  
borate (242mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-  
(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-  
dihydro-1H-1-benzazepine-4-carboxamide (436mg). To the  
10 solution was added potassium carbonate (299mg), and the  
mixture was stirred under argon atmosphere at room  
temperature for 30 minutes. To the mixture was added  
tetrakis(triphenylphosphine)palladium (42mg), and the  
mixture was heated to reflux under argon atmosphere for  
15 10 hours. The mixture was diluted with ethyl acetate,  
and washed with water and saturated brine, and the  
organic layer was dried with anhydrous magnesium sulfate.  
The solvent was evaporated under reduced pressure, and  
the residue was purified with silica gel column  
20 chromatography (30g, ethyl acetate : ethanol :  
triethylamine = 180 : 20 : 1) and recrystallized from  
ethanol/hexane to give 1-methyl-N-[4-[[N-methyl-N-  
(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(2-  
propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-  
25 carboxamide (Compound 12) (186mg, 35%) as yellow crystals.

Amman.  
B36

10018321-121201

mp 136 - 138°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.3 Hz), 1.65 (2H, sextet, J = 7.2 Hz), 1.69 - 1.76 (4H, m), 2.21 (3H, s), 2.57 - 2.72 (1H, m), 2.96 (2H, t, J = 4.4 Hz), 3.09 (3H, s), 3.32 - 3.43 (4H, m), 3.51 (2H, t, J = 6.8 Hz), 3.56 (2H, s), 3.81 (2H, t, J = 5.0 Hz), 4.01 - 4.06 (2H, m), 4.16 (2H, t, J = 4.9 Hz), 6.88 (1H, d, J = 8.4 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.6 Hz), 7.40 - 7.56 (8H, m).

IR (KBr) 1651, 1607, 1514, 1501, 1312, 1244, 1186 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>36</sub>H<sub>45</sub>N<sub>3</sub>O<sub>4</sub> (0.3H<sub>2</sub>O additive): C, 73.39; H, 7.80; N, 7.13. Found C, 73.12; H, 7.67; N, 7.08.

#### Working Example 13 (Production of Compound 13)

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved 4-(3-ethoxypropoxy)phenyl borate (250mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (450mg). To the solution was added potassium carbonate (308mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (43mg), and the mixture was refluxed under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was



evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (25g, ethyl acetate : ethanol : triethylamine = 100 : 10 : 1) and recrystallized from ethanol/hexane to give 7-[4-(3-ethoxypropoxy)phenyl]-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 13) (359mg, 66%) as yellow crystals.

mp 98 - 100°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.21 (3H, t, J = 6.9 Hz), 1.63 - 1.79 (4H, m), 2.07 (2H, quint, J = 6.3 Hz), 2.21 (3H, s), 2.54 - 2.75 (1H, m), 2.96 (2H, t, J = 4.4 Hz), 3.09 (3H, s), 3.31 - 3.43 (4H, m), 3.51 (2H, q, J = 7.0 Hz), 3.56 (2H, s), 3.62 (2H, t, J = 6.3 Hz), 4.00 - 4.07 (2H, m), 4.10 (2H, t, J = 6.2 Hz), 6.88 (1H, d, J = 8.6 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.6 Hz), 7.40 - 7.56 (3H, m), 7.40 (1H, s), 7.48 (2H, d, J = 9.0 Hz), 7.54 (2H, d, J = 8.6 Hz). IR (KBr) 1647, 1607, 1514, 1501, 1312, 1244, 1182, 1115cm<sup>-1</sup>. Anal. Calcd. for C<sub>36</sub>H<sub>45</sub>N<sub>3</sub>O<sub>4</sub> (0.2H<sub>2</sub>O additive): C, 73.62; H, 7.79; N, 7.15. Found C, 73.53; H, 7.63; N, 7.11.

#### Working Example 14 (Production of Compound 14)

In DMF (9.5ml) was dissolved 1-formyl-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (379mg). To the solution was added thionyl chloride (0.18ml), and the mixture was stirred at

room temperature for 30 minutes. Under reduced pressure,  
 the solvent was evaporated, and to the residue was added  
 THF (15.0ml). On the other hand, to 4-[[N-methyl-N-  
 (tetrahydro-2H-pyran-4-yl)amino]methyl]aniline  
 5 dihydrochloride (337mg) was added THF (10.0ml), and then  
 was added triethylamine (1.00ml). To the obtained  
 mixture was added dropwise at 0°C the previously prepared  
 acid chloride suspension, and the mixture was stirred at  
 room temperature for 15 hours. To the mixture was added  
 10 ethyl acetate, and the mixture was washed with water and  
 saturated brine. The organic layer was dried with  
 anhydrous magnesium sulfate. The solvent was evaporated  
 under reduced pressure, and the residue was purified with  
 silica gel column chromatography (35g, ethyl acetate →  
 15 ethyl acetate : ethanol = 10 : 1 → ethyl acetate :  
 ethanol : triethylamine = 100 : 10 : 1) and  
 recrystallized from ethanol to give 1-formyl-N-[4-[[N-  
 methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-  
 7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-  
 20 benzazepine-4-carboxamide (Compound 14) (459mg, 80%) as  
 white crystals.

mp 187 - 189°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J = 7.4 Hz), 1.57 -  
 1.74 (6H, m), 2.20 (3H, s), 2.56 - 2.72 (1H, m), 3.03 (2H,  
 25 t, J = 5.2 Hz), 3.37 (2H, td, J = 11.0, 2.8 Hz), 3.52 (2H,

Amen.  
 B37

10013331-131201

t, J = 6.8 Hz), 3.57 (2H, s), 3.82 (2H, t, J = 4.9 Hz), 3.92 (2H, t, J = 5.3 Hz), 4.01 - 4.07 (2H, m), 4.18 (2H, t, J = 4.9 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.19 (1H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.46 - 7.58 (7H, m), 7.67 (1H, s), 8.55 (1H, s).

IR (KBr) 1667, 1609, 1518, 1497, 1360, 1314, 1248, 824  $\text{cm}^{-1}$ .  
Anal. Calcd. for  $\text{C}_{36}\text{H}_{43}\text{N}_3\text{O}_5$ : C, 72.34; H, 7.25; N, 7.03.  
Found C, 72.39; H, 7.32; N, 7.08.

#### Working Example 15 (Production of Compound 15)

10 In DMF (6.5ml) was dissolved 1-methylsulfonyl-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (296mg). To the solution was added thionyl chloride (0.12ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, 15 the solvent was evaporated, and to the residue was added THF (15.0ml). On the other hand, to 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (234mg) was added THF (10.0ml), and then was added triethylamine (0.69ml). To the obtained 20 mixture was added dropwise at 0°C the previously prepared acid chloride suspension, and the mixture was stirred at room temperature for 3 hour. To the mixture was added ethyl acetate, and the mixture was washed with water and saturated brine. The organic layer was dried with 25 anhydrous magnesium sulfate. The solvent was evaporated

under reduced pressure, and the residue was purified with silica gel column chromatography (25g, ethyl acetate → ethyl acetate : ethanol : triethylamine = 100 : 10 : 1) and recrystallized from ethanol to give 1-methylsulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 15) (248mg, 58%) as white crystals.

mp 161 - 162°C.

10 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J = 7.3 Hz), 1.65 (2H, sextet, J = 7.1 Hz), 1.69 - 1.77 (4H, m), 2.21 (3H, s), 2.54 - 2.70 (1H, m), 2.88 (3H, s), 3.13 (2H, t, J = 5.0 Hz), 3.37 (2H, td, J = 11.4, 5.6 Hz), 3.52 (2H, t, J = 6.8 Hz), 3.57 (2H, s), 3.82 (2H, t, J = 4.8 Hz), 3.91 (2H, t, J = 5.7 Hz), 4.01 - 4.07 (2H, m), 4.18 (2H, t, J = 5.0 Hz), 7.00 - 7.04 (2H, m), 7.32 (2H, d, J = 8.4 Hz), 7.50 (2H, d, J = 8.8 Hz), 7.48 - 7.66 (7H, m).

15 IR (KBr) 1663, 1609, 1516, 1493, 1343, 1310, 1248, 1154, 667 cm<sup>-1</sup>.

20 Anal. Calcd. for C<sub>36</sub>H<sub>45</sub>N<sub>3</sub>O<sub>6</sub>S: C, 66.74; H, 7.00; N, 6.49. Found C, 66.56; H, 7.03; N, 6.36.

#### Working Example 16 (Production of Compound 16)

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved 4-(2-ethoxyethoxy)phenyl borate (339mg) and 7-bromo-1-ethyl-N-[4-[[N-methyl-N-

25

(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (537mg). To the solution was added potassium carbonate (357mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (50mg), and the mixture was heated to reflux under argon atmosphere for 14 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (35g, ethyl acetate → ethyl acetate : ethanol = 10 : 1 → ethyl acetate : ethanol : triethylamine = 100 : 10 : 0.5) and recrystallized from ethyl acetate/IPE to give 7-[4-(2-ethoxyethoxy)phenyl]-1-ethyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 16) (332mg, 53%) as yellow crystals. mp 114.5 - 116.5°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t, J = 6.9 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.63 - 1.76 (4H, m), 2.21 (3H, s), 2.59 - 2.69 (1H, m), 2.91 (2H, t, J = 4.8 Hz), 3.31 - 3.42 (4H, m), 3.44 (2H, q, J = 7.0 Hz), 3.57 (2H, s), 3.64 (2H, t, J = 6.9 Hz), 3.82 (2H, t, J = 4.8 Hz), 4.01 - 4.06 (2H, m),

4.16 (2H, t, J = 5.0 Hz), 6.91 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 9.2 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.40 (1H, s), 7.47 (2H, d, J = 9.2 Hz), 7.53 (2H, d, J = 8.4 Hz), 7.40 - 7.56 (3H, m).

5 IR (KBr) 1651, 1607, 1514, 1501, 1312, 1244, 1175, 1140, 1119  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{36}\text{H}_{45}\text{N}_3\text{O}_4$  (0.2 $\text{H}_2\text{O}$  additive): C, 73.62; H, 7.79; N, 7.15. Found C, 73.45; H, 7.85; N, 7.05.

Working Example 17 (Production of Compound 17)

10 In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved 4-(2-propoxyethoxy)phenyl borate (272mg) and 7-bromo-1-ethyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (404mg). To the  
15 solution was added potassium carbonate (269mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (37mg), and the mixture was heated to reflux under argon atmosphere for  
20 14 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column  
25 chromatography (30g, ethyl acetate  $\rightarrow$  ethyl acetate :

10018321.121201

ethanol = 10:1 → ethyl acetate : ethanol : triethylamine  
 = 100 : 10 : 0.5) and recrystallized from ethyl  
 acetate/IPE to give 1-ethyl-N-[4-[[N-methyl-N-  
 (tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(2-  
 5 propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-  
 carboxamide (Compound 17) (221mg, 46%) as yellow crystals.  
 mp 106 - 108°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.5 Hz), 1.32 (3H,  
 t, J = 6.9 Hz), 1.65 (2H, sextet, J = 7.1 Hz), 1.70 - 1.76  
 10 (4H, m), 2.21 (3H, s), 2.56 - 2.69 (1H, m), 2.92 (2H, t, J  
 = 4.0 Hz), 3.31 - 3.46 (6H, m), 3.51 (2H, t, J = 6.8 Hz),  
 3.56 (2H, s), 3.81 (2H, t, J = 4.9 Hz), 4.01 - 4.06 (2H, m),  
 4.16 (2H, t, J = 5.0 Hz), 6.92 (1H, d, J = 8.4 Hz), 6.98  
 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.8 Hz), 7.40 (1H, s),  
 15 7.47 (2H, d, J = 8.8 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.40 -  
 7.56 (3H, m).

IR (KBr) 2928, 1651, 1645, 1607, 1514, 1501, 1314, 1244,  
 1175 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>37</sub>H<sub>47</sub>N<sub>3</sub>O<sub>4</sub> (0.3H<sub>2</sub>O additive): C, 73.67; H,  
 20 7.95; N, 6.97. Found C, 73.52; H, 7.76; N, 6.95.

#### Working Example 18 (Production of Compound 18)

In a mixture of water : ethanol : toluene (1 : 1 :  
 10, v/v, 18.0ml) were dissolved 4-(2-butoxyethoxy)phenyl  
 borate (324mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-  
 25 (tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-

Amen.  
B38

dihydro-1H-1-benzazepine-4-carboxamide (440mg). To the  
 solution was added potassium carbonate (301mg), and the  
 mixture was stirred under argon atmosphere at room  
 temperature for 30 minutes. To the mixture was added  
 5 tetrakis(triphenylphosphine)palladium (42mg), and the  
 mixture was refluxed under argon atmosphere for 10 hours.  
 The mixture was diluted with ethyl acetate, and washed  
 with water and saturated brine, and the organic layer was  
 dried with anhydrous magnesium sulfate. The solvent was  
 10 evaporated under reduced pressure, and the residue was  
 purified with silica gel column chromatography (30g,  
 ethyl acetate → ethyl acetate : ethanol = 10 : 1 → ethyl  
 acetate : ethanol : triethylamine = 100 : 10 : 0.5) and  
 recrystallized from ethyl acetate/IPE to give 7-[4-(2-  
 15 butoxyethoxy)phenyl]-1-methyl-N-[4-[N-methyl-N-  
 (tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-  
 dihydro-1H-1-benzazepine-4-carboxamide (Compound 18)  
 (287mg, 53%) as yellow crystals.  
 mp 107 - 110°C.  
 20 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.39 (2H,  
 sextet, J = 7.3 Hz), 1.55 - 1.79 (6H, m), 2.21 (3H, s),  
 2.57 - 2.75 (1H, m), 2.96 (2H, t, J = 4.4 Hz), 3.09 (3H, s),  
 3.31 - 3.38 (2H, m), 3.37 (2H, td, J = 11.6, 2.7 Hz), 3.55  
 (2H, t, J = 6.6 Hz), 3.57 (2H, s), 3.81 (2H, t, J = 5.0 Hz),  
 25 4.00 - 4.08 (2H, m), 4.16 (2H, t, J = 4.9 Hz), 6.88 (1H, d,



J = 8.6 Hz), 6.96 - 7.01 (2H, m), 7.30 (2H, d, J = 8.4 Hz), 7.40 - 7.56 (4H, m), 7.48 (2H, d, J = 9.0 Hz), 7.54 (2H, d, J = 8.6 Hz).

IR (KBr) 2955, 2936, 1651, 1607, 1514, 1312, 1244, 1186cm<sup>-1</sup>.

5 Anal. Calcd. for C<sub>37</sub>H<sub>47</sub>N<sub>3</sub>O<sub>4</sub> (0.1H<sub>2</sub>O additive): C, 74.12; H, 7.93; N, 7.01. Found C, 73.90; H, 7.82; N, 7.12.

Working Example 19 (Production of Compound 19)

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved 4-(2-butoxyethoxy)phenyl borate (301mg) and 7-bromo-1-ethyl-N-[ 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (420mg). To the solution was added potassium carbonate (279mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (39mg), and the mixture was refluxed under argon atmosphere for 14 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (30g, ethyl acetate → ethyl acetate : ethanol = 10 : 1 → ethyl acetate : ethanol : triethylamine = 100 : 10 : 0.5) and recrystallized from ethyl acetate/IPE to give 7-[4-(2-

1001331-121201

butoxyethoxy)phenyl]-1-ethyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 19) (218mg, 42%) as yellow crystals.

5 mp 102 - 106°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.1 Hz), 1.32 (3H, t, J = 7.0 Hz), 1.39 (2H, sextet, J = 7.4 Hz), 1.54 - 1.76 (6H, m), 2.21 (3H, s), 2.54 - 2.72 (1H, m), 2.92 (2H, t, J = 4.6 Hz), 3.31 - 3.50 (6H, m), 3.55 (2H, t, J = 6.6 Hz), 10 3.57 (2H, s), 3.81 (2H, t, J = 4.9 Hz), 4.01 - 4.07 (2H, m), 4.16 (2H, t, J = 5.0 Hz), 6.92 (1H, d, J = 8.6 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.40 (1H, s), 7.44 - 7.56 (3H, m), 7.47 (2H, d, J = 9.0 Hz), 7.54 (2H, d, J = 8.4 Hz).

15 IR (KBr) 2953, 2932, 1651, 1605, 1514, 1501, 1406, 1314, 1244, 1175 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>38</sub>H<sub>49</sub>N<sub>3</sub>O<sub>4</sub> (0.2H<sub>2</sub>O additive): C, 74.16; H, 8.09; N, 6.83. Found C, 73.92; H, 8.19; N, 6.59.

#### Working Example 20 (Production of Compound 20)

20 In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v. 18.0ml) were dissolved 4-[(2-ethoxy)ethoxy]-3-fluorophenyl borate (355mg) and 7-bromo-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-  
25 carboxamide (517mg). To the solution was added potassium

carbonate (344mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (48mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (30g, ethyl acetate → ethyl acetate : ethanol = 10 : 1 → ethyl acetate : ethanol : triethylamine = 100 : 10 : 1) and recrystallized from ethanol to give 7-[4-(2-ethoxy)ethoxy-3-fluorophenyl]-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 20) (476mg, 76%) as white crystals. mp 188 - 191°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t, J = 7.1 Hz), 1.64 - 1.77 (4H, m), 2.20 (3H, s), 2.57 - 2.72 (1H, m), 3.04 (2H, t, J = 5.2 Hz), 3.37 (2H, td, J = 11.3, 2.9 Hz), 3.57 (2H, s), 3.63 (2H, q, J = 7.0 Hz), 3.85 (2H, t, J = 4.9 Hz), 3.92 (2H, t, J = 5.6 Hz), 4.01 - 4.07 (2H, m), 4.25 (2H, t, J = 4.9 Hz), 7.09 (1H, t, J = 8.6 Hz), 7.20 (1H, d, J = 8.2 Hz), 7.29 - 7.36 (2H, m), 7.32 (2H, d, J = 8.0 Hz), 7.45 (1H, s), 7.53 (2 H + 1H, d, J = 8.8 Hz), 7.56 (1H, s), 7.65

(1H, d,  $J = 2.2$  Hz), 8.55 (1H, s).

IR (KBr) 1669, 1501, 1358, 1314, 1269, 1238, 1198, 1138, 1125  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{35}\text{H}_{40}\text{FN}_3\text{O}_4$ : C, 69.86; H, 6.70; N, 6.98.

5 Found C, 69.66; H, 6.40; N, 6.71.

Working Example 21 (Production of Compound 21)

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved 3-chloro-4-(2-ethoxy)ethoxyphenyl borate (280mg) and 7-bromo-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (380mg). To the solution was added potassium carbonate (253mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (35mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (25g, ethyl acetate  $\rightarrow$  ethyl acetate : ethanol = 10 : 1  $\rightarrow$  ethyl acetate : ethanol : triethylamine = 100 : 10 : 0.5) and recrystallized from ethanol to give 7-[3-chloro-4-(2-ethoxy)ethoxyphenyl]-1-

Amen.  
B39

100183221.121201

formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 21) (342mg, 73%) as white crystals. mp 198 - 200°C.

- 5 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.26 (3H, t, J = 6.9 Hz), 1.64 - 1.76 (4H, m), 2.20 (3H, s), 2.57 - 2.69 (1H, m), 3.04 (2H, t, J = 5.2 Hz), 3.37 (2H, td, J = 11.1, 2.9 Hz), 3.57 (2H, s), 3.67 (2H, q, J = 7.0 Hz), 3.88 (2H, t, J = 5.0 Hz), 3.91 (2H, t, J = 6.0 Hz), 4.01 - 4.06 (2H, m), 4.24 (2H, t, J = 4.9 Hz), 7.05 (1H, d, J = 8.4 Hz), 7.20 (1H, d, J = 8.2 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.43 (1H, dd, J = 8.6, 2.4 Hz), 7.44 (1H, s), 7.54 (2 H + 1H, d, J = 8.4 Hz), 7.56 (1H, s), 7.61 (1H, d, J = 2.2 Hz), 7.65 (1H, d, J = 2.2 Hz), 8.55 (1H, s).
- 10
- 15 IR (KBr) 1669, 1599, 1516, 1493, 1360, 1314, 1292, 1260, 1140, 1065 cm<sup>-1</sup>.
- Anal. Calcd. for C<sub>35</sub>H<sub>40</sub>ClN<sub>3</sub>O<sub>5</sub>: C, 68.00; H, 6.52; N, 6.80. Found C, 67.71; H, 6.43; N, 6.71.

#### Working Example 22 (Production of Compound 22)

- 20 In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved 4-(3-propoxy)propoxyphenyl borate (270mg) and 7-bromo-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-
- 25 carboxamide (377mg). To the solution was added potassium

carbonate (251mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (35mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (25g, ethyl acetate → ethyl acetate : ethanol = 10 : 1 → ethyl acetate : ethanol : triethylamine = 100 : 10 : 0.5) and recrystallized from ethanol to give 1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(3-propoxy)propoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 22) (304mg, 66%) as white crystals. mp 174 - 177°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.92 (3H, t, J = 7.3 Hz), 1.60 (2H, sextet, J = 7.1 Hz), 1.69 - 1.76 (4H, m), 2.08 (2H, quint, J = 6.2 Hz), 2.20 (3H, s), 2.59 - 2.69 (1H, m), 3.03 (2H, t, J = 4.9 Hz), 3.31 - 3.41 (2H, m), 3.41 (2H, t, J = 6.6 Hz), 3.57 (2H, s), 3.61 (2H, t, J = 6.0 Hz), 3.92 (2H, t, J = 5.3 Hz), 4.01 - 4.09 (2H, m), 4.12 (2H, t, J = 6.4 Hz), 7.00 (2H, d, J = 8.8 Hz), 7.19 (1H, d, J = 8.0 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.46 (1H, s), 7.51 (2H, d, J = 8.4 Hz),

7.54 (2H, d,  $J = 8.4$  Hz), 7.49 - 7.58 (2H, m), 7.67 (1H, d,  $J = 1.8$  Hz), 8.54 (1H, s).

IR (KBr) 2940, 1669, 1607, 1516, 1497, 1360, 1314, 1248, 1119  $\text{cm}^{-1}$ .

5 Anal. Calcd. for  $\text{C}_{37}\text{H}_{45}\text{N}_3\text{O}_5$ : C, 72.64; H, 7.41; N, 6.87.  
Found C, 72.46; H, 7.62; N, 6.95.

#### Working Example 23 (Production of Compound 23)

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved 3-ethoxy-4-(2-  
10 propoxy)ethoxyphenyl borate (324mg) and 7-bromo-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (401mg). To the solution was added potassium carbonate (267mg), and the mixture was stirred under  
15 argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (37mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine,  
20 and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (25g, ethyl acetate  $\rightarrow$  ethyl acetate : ethanol = 10 : 1  $\rightarrow$  ethyl acetate : ethanol : triethylamine = 100 : 10 : 0.5) and recrystallized from  
25

10048324-121201  
T02T2T-T2E8FOOT

ethyl acetate/IPE to give 7-[3-ethoxy-4-(2-propoxy)ethoxyphenyl]-1-formyl-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 23)

5 (317mg, 61%) as white crystals.

mp 117 - 119°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.3 Hz), 1.48 (3H, t, J = 6.9 Hz), 1.64 (2H, sextet, J = 7.2 Hz), 1.64 - 1.76 (4H, m), 2.20 (3H, s), 2.57 - 2.70 (1H, m), 3.03 (2H, t, J = 3.6 Hz), 3.37 (2H, td, J = 11.2, 2.7 Hz), 3.53 (2H, t, J = 6.7 Hz), 3.56 (2H, s), 3.84 (2H, t, J = 5.1 Hz), 3.92 (2H, t, J = 5.3 Hz), 4.01 - 4.07 (2H, m), 4.16 (2H, q, J = 7.1 Hz), 4.22 (2H, t, J = 5.2 Hz), 7.03 (1H, d, J = 8.8 Hz), 7.10 (1H, s), 7.11 (1H, dd, J = 8.4, 2.2 Hz), 7.18 (1H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.50 (2H, d, J = 8.4 Hz), 7.54 (1H, d, J = 8.4 Hz), 7.57 (1H, d, J = 2.6 Hz), 7.60 (1H, s), 7.57 (1H, d, J = 1.8 Hz), 8.54 (1H, s).

IR (KBr) 2942, 1671, 1597, 1514, 1499, 1408, 1360, 1316, 1254, 1202, 1140 cm<sup>-1</sup>.

20 Anal. Calcd. for C<sub>38</sub>H<sub>47</sub>N<sub>3</sub>O<sub>6</sub> (0.1H<sub>2</sub>O additive): C, 70.92; H, 7.39; N, 6.53. Found C, 70.71; H, 7.36; N, 6.47.

#### Working Example 24 (Production of Compound 24)

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved (2,3-dihydro-1,4-benzodioxin-6-yl) borate (221mg) and 7-bromo-1-methyl-N-

25



[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (397mg). To the solution was added potassium carbonate (272mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (38mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (35g, ethyl acetate : ethanol = 20 : 1) and recrystallized from ethanol to give 7-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 24) (215mg, 49%) as yellow crystals.

mp 164 - 165°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.63 - 1.76 (4H, m), 2.20 (3H, s), 2.53 - 2.73 (1H, m), 2.95 (2H, t, J = 4.4 Hz), 3.07 (3H, s), 3.31 - 3.43 (4H, m), 3.56 (2H, s), 4.01 - 4.07 (2H, m), 4.29 (4H, s), 6.86 (1H, d, J = 8.4 Hz), 6.90 (1H, d, J = 9.6 Hz), 7.05 (1H, dd, J = 10.4, 2.2 Hz), 7.07 (1H, s), 7.29 (2H, d, J = 8.6 Hz), 7.37 - 7.55 (3H, m), 7.54 (2H, d,

$J = 8.6 \text{ Hz}$ ), 7.62 (1H, s).

IR (KBr) 2948, 1644, 1597, 1514, 1497, 1406, 1312, 1283, 1246, 1188, 1071, 810, 733  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{33}\text{H}_{37}\text{N}_3\text{O}_4$  (0.2 $\text{H}_2\text{O}$  additive): C, 72.96; H, 6.94; N, 7.73. Found C, 72.86; H, 6.91; N, 7.70.

Working Example 25 (Production of Compound 25)

In a mixture of water : ethanol : toluene (1 : 1 : 10. v/v, 18.0ml) were dissolved 4-(2-ethoxyethoxy)phenyl borate (246mg) and 7-bromo-1-propyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (400mg). To the solution was added potassium carbonate (259mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (36mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (30g, ethyl acetate  $\rightarrow$  ethyl acetate : ethanol = 10 : 1) and recrystallized from ethyl acetate-IPE to give 7-[4-(2-ethoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1-

propyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide

(Compound 25) (216mg, 46%) as yellow crystals.

mp 144 - 147°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.99 (3H, t, J = 7.4 Hz), 1.26 (3H, t, J = 6.9 Hz), 1.63 - 1.84 (6H, m), 2.20 (3H, s), 2.56 - 2.69 (1H, m), 2.91 (2H, t, J = 4.4 Hz), 3.28 - 3.43 (6H, m), 3.56 (2H, s), 3.62 (2H, q, J = 7.0 Hz), 3.81 (2H, t, J = 4.9 Hz), 4.01 - 4.06 (2H, m), 4.16 (2H, t, J = 4.8 Hz), 6.90 (1H, d, J = 8.6 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.37 - 7.55 (8H, m).

IR (KBr) 2957, 2940, 1644, 1605, 1499, 1406, 1312, 1240, 1177, 1140, 1121 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>37</sub>H<sub>47</sub>N<sub>3</sub>O<sub>4</sub>: C, 74.34; H, 7.92; N, 7.02.

Found C, 74.13; H, 7.76; N, 7.17.

#### Working Example 26 (Production of Compound 26)

In a mixture of water : ethanol : toluene (1 : 1 : 10, v/v, 18.0ml) were dissolved 4-(2-propoxyethoxy)phenyl borate (260mg) and 7-bromo-1-propyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (396mg). To the solution was added potassium carbonate (256mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (36mg), and the mixture was heated to reflux under argon atmosphere for

10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and  
 5 the residue was purified with silica gel column chromatography (25g, ethyl acetate → ethyl acetate : ethanol = 10 : 1) and recrystallized from ethyl acetate-IPE to give N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-1-  
 10 propyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 26) (252mg, 53%) as yellow crystals.

mp 128 - 130°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.5 Hz), 0.99 (3H, t, J = 7.6 Hz), 1.59 - 1.81 (8H, m), 2.20 (3H, s), 2.56 -  
 15 2.69 (1H, m), 2.92 (2H, t-like), 3.28 - 3.43 (6H, m), 3.51 (2H, t, J = 6.7 Hz), 3.56 (2H, s), 3.81 (2H, t, J = 5.0 Hz), 4.01 - 4.06 (2H, m), 4.16 (2H, t, J = 5.0 Hz), 6.90 (1H, d, J = 8.4 Hz), 6.98 (2H, d, J = 8.4 Hz), 7.29 (2H, d, J = 8.8 Hz), 7.38 - 7.55 (8H, m).

20 IR (KBr) 2957, 2940, 1644, 1605, 1499, 1406, 1312, 1240, 1177, 1140, 1121 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>39</sub>H<sub>49</sub>N<sub>3</sub>O<sub>4</sub>: C, 74.60; H, 8.07; N, 6.87.  
 Found C, 74.31; H, 8.21; N, 7.12.

#### Working Example 27 (Production of Compound 27)

25 In a mixture of water : ethanol : toluene (1 : 1 :

10, v/v, 24.0ml) were dissolved 4-(2-butoxyethoxy)phenyl borate (519mg) and 7-bromo-1-propyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (745mg). To the solution was added potassium carbonate (482mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (67mg), and the mixture was refluxed under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (35g, ethyl acetate → ethyl acetate : ethanol = 10 : 1) and recrystallized from ethyl acetate-IPE to give 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1-propyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 27) (453mg, 50%) as yellow crystals.

mp 122 - 124°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.1 Hz), 0.99 (3H, t, J = 7.3 Hz), 1.39 (2H, sextet, J = 7.2 Hz), 1.54 - 1.80 (8H, m), 2.20 (3H, s), 2.53 - 2.71 (1H, m), 2.91 (2H, t, J = 4.0 Hz), 3.27 - 3.43 (6H, m), 3.52 - 3.58 (4H, m), 3.80

(2H, t, J = 5.0 Hz), 4.01 - 4.06 (2H, m), 4.15 (2H, t, J = 4.7 Hz), 6.89 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.37 - 7.59 (8H, m).

IR (KBr) 2957, 2940, 1644, 1605, 1499, 1406, 1312, 1240, 1177, 1140, 1121  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{39}\text{H}_{51}\text{N}_3\text{O}_4$ : C, 74.85; H, 8.21; N, 6.71. Found C, 74.64; H, 8.36; N, 6.93.

#### Working Examples 28 (Production of Compound 28)

In 1N hydrochloric acid (50ml) and THF (50ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (1.4g). The solution was refluxed for 4.5 hours, concentrated, neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 28) (1.0g) as yellow crystals.

mp 119 - 123°C.

$^1\text{H}$ -NMR ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.93 (3H, t, J = 7.3 Hz), 1.34 - 1.75 (8H, m), 2.21 (3H, s), 2.60 - 2.65 (1H, m), 2.96 (2H, t-like), 3.32 - 3.58 (8H, m), 3.80 (2H, t, J = 5.0 Hz), 4.01

10018321-121201

- 4.07 (2H, m), 4.16 (2H, t,  $J = 5.0$  Hz), 4.57 (1H, br), 6.70 (1H, d,  $J = 8.2$  Hz), 6.98 (2H, d,  $J = 9.0$  Hz), 7.26 - 7.32 (4H, m), 7.43 - 7.56 (5H, m).

IR (KBr)  $\nu$ : 3328, 2946, 2851, 1651, 1609, 1514, 1499  $\text{cm}^{-1}$ .

5     Anal. Calcd. for  $\text{C}_{36}\text{H}_{45}\text{N}_3\text{O}_4 \cdot 0.25\text{H}_2\text{O}$ : C, 73.50; H, 7.80; N, 7.14. Found C, 73.54; H, 7.79; N, 7.15.

Working Example 29 (Production of Compound 29)

10     In DMF (5ml) was dissolved 1-propionyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.2g). Under ice-cooling, to the solution was added thionyl chloride (0.09ml). The mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure. In THF (15ml) was dissolved the residue, which was added  
15     dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.15g) and triethylamine (0.34ml) in THF (5ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced  
20     solvent. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give crude crystals, which were recrystallized from  
25     ethyl acetate-hexane to give 1-propionyl-7-[4-(2-

propoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 29) (0.1g) as pale yellow crystals.

5 mp 167 - 169°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.95 (3H, t, J = 7.3 Hz), 1.08 (3H, t, J = 7.5 Hz), 1.58 - 1.75 (6H, m), 2.12 - 2.21 (1H, m), 2.21 (3H, s), 2.40 - 2.75 (2H, m), 2.75 - 3.00 (2H, m), 3.10 - 3.30 (1H, m), 3.37 (2H, dt, J = 2.8, 11.2 Hz), 3.52 (2H, t, J = 6.7 Hz), 3.58 (2H, s), 3.82 (2H, t, J = 4.8 Hz), 4.01 - 4.06 (2H, m), 4.19 (2H, t, J = 4.8 Hz), 4.81 - 4.88 (1H, m), 7.03 (2H, d, J = 8.8 Hz), 7.24 - 7.34 (3H, m), 7.50 - 7.56 (6H, m), 7.67 (1H, s).

IR (KBr) ν: 2944, 1653 cm<sup>-1</sup>.

15 Anal. Calcd. for C<sub>38</sub>H<sub>47</sub>N<sub>3</sub>O<sub>5</sub>·0.5H<sub>2</sub>O: C, 71.90; H, 7.62; N, 6.62. Found C, 71.84; H, 7.48; N, 6.71.

~~Working Example 30 (Production of Compound 30)~~

*Amen. B40*

~~In DMF (6ml) was dissolved 1-butyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.30g). Under ice-cooling, to the mixture was added thionyl chloride (0.15ml). The mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure. In THF (20ml) was suspended the residue, and the suspension was added dropwise to a solution of 4-[N-methyl-N-~~

20

25



(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.17g) and triethylamine (0.42ml) in THF (5ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced solvent. Water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine). The material was dissolved in ethyl acetate-ethanol, and 6N hydrochloric acid was added to the solution. The solvent was evaporated. Diethyl ether was added to the residue, and the precipitates were filtered to give 1-butyl-7-[4-(2-propoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide dihydrochloride (Compound 30) (0.36g) as pale yellow amorphous.

<sup>1</sup>H-NMR (δ ppm, DMSO-d<sub>6</sub>) 0.84 - 1.02 (6H, m), 1.30 - 1.45 (2H, m), 1.49 - 1.70 (4H, m), 1.70 - 1.95 (2H, m), 1.95 - 2.20 (2H, m), 2.58 (3H, d, J = 5.0 Hz), 2.80 - 2.85 (2H, m), 3.20 - 3.46 (8H, m), 3.66 - 3.84 (3H, m), 3.96 - 4.14 (3H, m), 4.12 (2H, t, J = 4.7 Hz), 4.39 - 4.45 (1H, m), 6.93 - 7.02 (3H, m), 7.41 - 7.63 (7H, m), 7.81 (2H, d, J = 8.4 Hz),

10.00 (1H, s), 10.22 (1H, br).

IR (KBr)  $\nu$ : 2691, 2930, 2872, 1653, 1609, 1518, 1501  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{39}\text{H}_{51}\text{N}_3\text{O}_4 \cdot 2\text{HCl} \cdot \text{H}_2\text{O}$ : C, 65.35; H, 7.73; N, 5.86. Found C, 65.04; H, 7.88; N, 5.66.

5           Working Example 31 (Production of Compound 31)

10048324.124304  
A mixture of 7-bromo-1-cyclopropyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.45g), 4-(2-butoxyethoxy)phenyl borate (0.23g), 1M potassium carbonate solution (1.5ml), ethanol (1.5ml) and toluene (25ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.05g), and the mixture was refluxed for 3 hours under argon atmosphere and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized to give 7-[4-(2-butoxyethoxy)phenyl]-1-cyclopropyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 31) (0.25g) as pale yellow crystals.

mp 117 - 120°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.55 - 0.62 (2H, m), 0.85 - 0.93 (2H, m), 0.93 (3H, t, J = 7.0 Hz), 1.21 - 1.76 (8H, m), 2.20 (3H, s), 2.56 - 2.76 (2H, m), 2.90 (2H, t-like), 3.34 (2H, dt, J = 8.0, 11.4 Hz), 3.43 - 3.59 (6H, m), 3.80 (2H, t, J = 5.0 Hz), 4.00 - 4.06 (2H, m), 4.16 (2H, t, J = 5.0 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.25 - 7.36 (3H, m), 7.42 - 7.54 (7H, m).

Anal. Calcd. for C<sub>39</sub>H<sub>49</sub>N<sub>3</sub>O<sub>4</sub>: C, 75.09; H, 7.92; N, 6.74.

Found C, 75.09; H, 8.14; N, 6.78.

~~Working Example 32 (Production of Compound 32)~~

~~In DMF (4ml) was dissolved 1-benzyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.15g). Under ice-cooling, to the mixture was added thionyl chloride (0.06ml). The mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure. In THF (25ml) was dissolved the residue, the solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.09g) and triethylamine (0.23ml) in THF (10ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced solvent. Water was added to the mixture, the mixture was extracted with ethyl acetate. The organic layer was~~

*Ammon.  
B<sub>4</sub>*

FOOT-41-12100

washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine).

- 5 The material was dissolved in ethyl acetate, and 4N hydrochloric acid-ethyl acetate was added to the solution. The solvent was evaporated to give 1-benzyl-7-[4-(2-propoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide hydrochloride (Compound 32)
- 10 (0.14g) as yellow amorphous.
- <sup>1</sup>H-NMR (δ ppm, DMSO-d<sub>6</sub>) 0.87 (3H, t, J = 7.3 Hz), 1.48 - 1.59 (2H, m), 1.65 - 2.15 (4H, m), 2.57 (3H, d, J = 4.8 Hz), 2.81 (2H, s), 3.25 - 3.45 (7H, m), 3.98 - 4.13 (5H, m), 4.39 - 4.46 (1H, m), 4.66 (2H, s), 6.86 (1H, d, J = 8.8 Hz), 6.99 (2H, d, J = 8.8 Hz), 7.27 - 7.57 (11H, m), 7.67 (1H, s), 7.81 (2H, d, J = 8.4 Hz), 10.04 (1H, s), 10.44 (1H, br).
- 15 IR (KBr) v: 2963, 2868, 1655, 1607, 1518, 1499 cm<sup>-1</sup>.
- Anal. Calcd. for C<sub>42</sub>H<sub>49</sub>N<sub>3</sub>O<sub>4</sub>·HCl·1.5H<sub>2</sub>O: C, 69.74; H, 7.39; N, 5.81. Found C, 69.35; H, 7.40; N, 5.84.
- 20

#### Working Example 33 (Production of Compound 33)

- In THF (5ml) was dissolved 1-benzyl-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.3g). Under ice-cooling, to the
- 25 solution were added oxalyl (0.11ml) and DMF (catalytic

amount). The mixture was stirred at room temperature for 30 minutes, and the solvent was evaporated under reduced pressure. In THF (25ml) was dissolved the residue, the solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.15g) and triethylamine (0.44ml) in THF (10 ml), under ice-cooling. The mixture was stirred at room temperature under nitrogen atmosphere and the solvent was evaporated under reduced pressure. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified by silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 1-benzyl-7-[4-(2-butoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 33) (0.26g) as pale yellow crystals.

mp 127 - 131°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.1 Hz), 1.30 - 1.75 (8H, m), 2.21 (3H, s), 2.55 - 2.70 (1H, m), 2.85 (2H, t-like), 3.31 - 3.38 (4H, m), 3.52 - 3.58 (4H, m), 3.80 (2H, t, J = 4.9 Hz), 4.01 - 4.05 (2H, m), 4.16 (2H, t, J = 4.9

Hz), 4.61 (2H, s), 6.90 (1H, d,  $J = 8.4$  Hz), 6.98 (2H, d,  $J = 8.8$  Hz), 7.26 - 7.56 (14H, m).

IR (KBr)  $\nu$ : 2934, 2851, 1651, 1601, 1514, 1501  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{43}\text{H}_{51}\text{N}_3\text{O}_4 \cdot 0.25\text{H}_2\text{O}$ : C, 76.13; H, 7.65; N, 6.19. Found C, 76.19; H, 7.55; N, 6.19.

Working Example 34 (Production of Compound 34)

In THF (3ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-cyclohexylmethyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.25g). Under ice-cooling, to the solution were added oxalyl chloride (0.09ml) and DMF (catalytic amount). The mixture was stirred at room temperature for 1 hour, and the solvent was evaporated under reduced pressure. In THF (25ml) was dissolved the residue, and the solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.14g) and triethylamine (0.36ml) in THF (5 ml), under ice-cooling. The mixture was stirred at room temperature under nitrogen atmosphere and the solvent was evaporated under reduced pressure. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give crude crystals, which were recrystallized from diethyl ether-ethyl acetate-hexane to give 7-[4-(2-

butoxyethoxy)phenyl]-1-cyclohexylmethyl-N-[4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 34) (0.28g) as pale yellow crystals.

5 mp 115 - 117°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 0.93 - 1.84 (19H, m), 2.21 (3H, s), 2.58 - 2.66 (1H, m), 2.91 (2H, t-like), 3.22 (2H, d, J = 6.6 Hz), 3.30 - 3.46 (4H, m), 3.50 - 3.58 (4H, m), 3.80 (2H, t, J = 4.9 Hz), 4.01 - 4.06 (2H, m), 4.16 (2H, t, J = 4.9 Hz), 6.91 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.37 - 7.56 (7H, m).

IR (KBr) ν: 2924, 2849, 1651, 1605, 1516, 1499 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>43</sub>H<sub>57</sub>N<sub>3</sub>O<sub>4</sub>: C, 75.96; H, 8.45; N, 6.18.

15 Found C, 75.93; H, 8.58; N, 6.21.

#### Working Example 35 (Production of Compound 35)

In THF (5ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-cyclopropylmethyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.35g). Under ice-cooling, to the solution were added oxalyl chloride (0.14ml) and DMF (catalytic amount). The mixture was stirred at room temperature for 1 hour, and the solvent was evaporated under reduced pressure. In THF (25ml) was dissolved the residue, and the solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-

20

25

pyran-4-yl)aminomethyl]aniline (0.20g) and triethylamine (0.56ml) in THF (10 ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere and the solvent was evaporated under reduced pressure. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 7-[4-(2-butoxyethoxy)phenyl]-1-cyclopropylmethyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 35) (0.36g) as yellow crystals.

mp 92 - 94°C.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.26 - 0.33 (2H, m), 0.60 - 0.69 (2H, m), 0.93 (3H, t,  $J = 7.4$  Hz), 1.05 - 1.18 (1H, m), 1.22 - 2.05 (8H, m), 2.21 (3H, s), 2.59 - 2.67 (1H, m), 2.95 (2H, t-like), 3.25 (2H, d,  $J = 6.2$  Hz), 3.32 - 3.58 (8H, m), 3.80 (2H, t,  $J = 5.0$  Hz), 3.93 - 4.18 (4H, m), 6.95 - 7.00 (3H, m), 7.29 (2H, d,  $J = 8.8$  Hz), 7.41 - 7.58 (7H, m).

IR (KBr)  $\nu$ : 3289, 2940, 2870, 1651, 1607, 1516, 1499  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{40}\text{H}_{51}\text{N}_3\text{O}_4$ : C, 75.32; H, 8.06; N, 6.59.



Found C, 75.21; H, 8.12; N, 6.49.

Working Example 36 (Production of Compound 36)

In THF (5ml) was dissolved 1-cyclopropylmethyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.25g). Under ice-cooling, to the solution were added oxalyl chloride (0.11ml) and DMF (catalytic amount). The mixture was stirred at room temperature for 1 hour, and the solvent was evaporated under reduced pressure. In THF (25ml) was dissolved the residue, and the solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.14g) and triethylamine (0.41ml) in THF (5ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere and the solvent was evaporated under reduced pressure. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine), which was dissolved in ethyl acetate. To the solution was added 4N hydrochloric acid-ethyl acetate, and the solvent was evaporated to give 1-cyclopropylmethyl-7-[4-(2-propoxyethoxy)phenyl]-N-[4-[[N-methyl-N-tetrahydro-2H-

pyran-4-yl]amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide dihydrochloride (Compound 36) (0.32g) as pale yellow amorphous.

<sup>1</sup>H-NMR (δ ppm, DMSO-d<sub>6</sub>) 0.29 - 0.31 (2H, m), 0.54 - 0.57 (2H, m), 0.88 (2H, t, J = 7.5 Hz), 1.06 - 1.13 (1H, m), 1.45 - 1.63 (2H, m), 1.70 - 2.20 (4H, m), 2.57 (3H, d, J = 4.8 Hz), 2.89 (2H, br), 3.25 - 3.46 (9H, m), 3.69 - 3.74 (2H, m), 4.10 - 4.14 (5H, m), 4.37 - 4.45 (1H, m), 7.00 (2H, d, J = 8.8 Hz), 7.03 - 7.11 (1H, m), 7.44 - 7.59 (6H, m), 7.68 (1H, s), 7.81 (2H, d, J = 8.6 Hz), 10.07 (1H, s), 10.63 (1H, br).

Working Example 37 (Production of Compound 37)

In THF (5ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-cyclobutylmethyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.25g). Under ice-cooling, to the solution were added oxalyl chloride (0.1ml) and DMF (catalytic amount). The mixture was stirred at room temperature for 1 hour, and the solvent was evaporated under reduced pressure. In THF (25ml) was dissolved the residue, the solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.13g) and triethylamine (0.4ml) in THF (5ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere and the solvent was evaporated under reduced pressure. To the residue was added water, and the mixture was

extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine), which was dissolved in ethyl acetate. To the solution was added 4N hydrochloric acid-ethyl acetate, and the solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-cyclobutylmethyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide dihydrochloride (Compound 37) (0.27g) as pale yellow amorphous.

<sup>1</sup>H-NMR (δ ppm, DMSO-d<sub>6</sub>) 0.89 (3H, t, J = 7.1 Hz), 1.24 - 1.58 (4H, m), 1.73 - 2.15 (1H, m), 2.57 (3H, d, J = 4.8 Hz), 2.60 - 2.85 (3H, m), 3.20 - 3.49 (10H, m), 3.96 - 4.13 (5H, m), 4.38 - 4.44 (1H, m), 6.97 - 7.02 (3H, m), 7.40 - 7.63 (7H, m), 7.80 (2H, d, J = 8.8 Hz), 10.02 (1H, s), 10.41 (1H, s).

Anal. Calcd. for C<sub>41</sub>H<sub>53</sub>N<sub>3</sub>O<sub>4</sub>·2HCl·1.5H<sub>2</sub>O: C, 65.50; H, 7.78; N, 5.59. Found C, 65.51; H, 7.77; N, 5.24.

#### Working Example 38 (Production of Compound 38)

In DMF (6ml) was dissolved 1-phenyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.2g). Under ice-cooling, to the mixture was added thionyl chloride (0.08ml). The mixture

was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure. In THF (20ml) was suspended the residue, the suspension was added dropwise to a solution of 4-[N-methyl-N-

5 (tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.12g) and triethylamine (0.31ml) in THF (5ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced pressure. Water was added to the mixture,

10 the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated, the residue was purified with silica gel column chromatography (ethyl acetate/methanol/

15 triethylamine), which was dissolved in ethyl acetate-ethanol, 4N hydrochloric acid-ethyl acetate was added to the solution, and the solvent was evaporated to give 1-phenyl-7-[4-(2-propoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-

20 dihydro-1H-1-benzazepine-4-carboxamide hydrochloride (Compound 38) (0.17g) as yellow crystals.

mp 223 - 224°C.

<sup>1</sup>H-NMR (δ ppm, DMSO-d<sub>6</sub>) 0.88 (3H, t, J = 7.3 Hz), 1.45 - 1.60 (2H, m), 1.70 - 1.95 (2H, m), 1.95 - 2.15 (2H, m),

25 2.58 (3H, d, J = 4.8 Hz), 2.84 (2H, br), 3.22 - 3.46 (4H,

10018321-121001  
m), 3.72 (2H, t, J = 4.7 Hz), 3.75 - 4.12 (5H, m), 4.15 (2H, t, J = 4.7 Hz), 4.39 - 4.46 (1H, m), 6.80 - 6.90 (1H, m), 6.98 - 7.07 (4H, m), 7.20 - 7.30 (3H, m), 7.47 - 7.57 (4H, m), 7.65 (2H, d, J = 8.8 Hz), 7.79 (2H, d, J = 8.8 Hz),  
5 7.85 (1H, s), 9.96 (1H, br), 10.07 (1H, s).

IR (KBr)  $\nu$ : 2961, 2928, 2863, 1651, 1520, 1495  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{41}\text{H}_{47}\text{N}_3\text{O}_4 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$ : C, 71.23; H, 7.14; N, 6.08. Found C, 71.56; H, 7.17; N, 6.18.

Working Example 39 (Production of Compound 39)

10 In THF (5ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-phenyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.25g). Under ice-cooling, to the solution were added oxalyl chloride (0.1ml) and DMF (catalytic amount). The mixture was stirred at room  
15 temperature for 1 hour, and the solvent was evaporated under reduced pressure. In THF (25ml) was suspended the residue, the suspension was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.13g) and triethylamine (0.38ml)  
20 in THF (5ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere and the solvent was evaporated under reduced pressure. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was  
25 washed with water and saturated brine, and dried with

anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give 7-[4-(2-butoxyethoxy)phenyl]-1-phenyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 39) (0.21g) as yellow amorphous.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.27 - 1.49 (2H, m), 1.55 - 1.74 (6H, m), 2.19 (3H, s), 2.58 - 2.66 (1H, m), 2.93 (2H, t, J = 4.8 Hz), 3.36 (2H, dt, J = 3.2, 10.8 Hz), 3.52 - 3.59 (4H, m), 3.81 (2H, t, J = 5.0 Hz), 3.89 (2H, t, J = 4.8 Hz), 4.00 - 4.06 (2H, m), 4.17 (2H, t, J = 5.0 Hz), 6.88 - 7.02 (5H, m), 7.21 - 7.30 (4H, m), 7.41 (1H, dd, J = 2.2, 8.6 Hz), 7.48 - 7.53 (6H, m), 7.64 (1H, d, J = 2.2 Hz).

IR (KBr) v: 2953, 2934, 2847, 1653, 1595, 1520, 1495 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>42</sub>H<sub>49</sub>N<sub>3</sub>O<sub>4</sub> · 0.25H<sub>2</sub>O: C, 75.93; H, 7.51; N, 6.32. Found C, 75.80; H, 7.40; N, 6.30.

#### Working Example 40 (Production of Compound 40)

In THF (5ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(3-methoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.15g). Under ice-cooling, to the solution were added oxalyl chloride (0.06ml) and DMF (catalytic amount). The mixture was stirred at room temperature for 30 minutes, and the

20

J = 8.8 Hz), 7.14 - 7.30 (3H, m), 7.40 - 7.54 (7H, m), 7.64 (1H, d, J = 1.8 Hz).

IR (KBr)  $\nu$ : 2955, 2845, 1661, 1595, 1516, 1493  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{43}\text{H}_{51}\text{N}_3\text{O}_5$ : C, 74.86; H, 7.45; N, 6.09.

5 Found C, 74.52; H, 7.66; N, 6.19.

Working Example 41 (Production of Compound 41)

In THF (5ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(4-methoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.2g). Under ice-cooling, to the solution were added oxalyl chloride (0.08ml) and DMF (catalytic amount). The mixture was stirred at room temperature for 1 hour, and the solvent was evaporated under reduced pressure. In THF (20ml) was dissolved the residue, and the solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.1g) and triethylamine (0.3ml) in THF (5ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere and the solvent was evaporated under reduced pressure. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/

10018341401  
FOOT-2288001



triethylamine) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(4-methoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 41) (0.22g) as yellow amorphous.

5 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.1 Hz), 1.26 - 1.48 (2H, m), 1.54 - 1.74 (6H, m), 2.20 (3H, s), 2.58 - 2.66 (1H, m), 2.90 (2H, t-like), 3.37 (2H, dt, J = 2.2, 12.7 Hz), 3.52 - 3.58 (4H, m), 3.78 - 3.83 (7H, m), 4.01 - 4.06 (2H, m), 4.16 (2H, t, J = 4.9 Hz), 6.85 - 7.05 (7H, m), 7.26 -  
10 7.34 (2H, m), 7.46 - 7.59 (7H, m).

#### Working Example 42 (Production of Compound 42)

In THF (5ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.2g). Under ice-  
15 cooling, to the solution were added oxalyl chloride (0.05ml) and DMF (catalytic amount). The mixture was stirred at room temperature for 1 hour, and the solvent was evaporated under reduced pressure. In THF (20ml) was dissolved the residue, and the solution was added  
20 dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.11g) and triethylamine (0.3ml) in THF (5ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere and the solvent was evaporated under reduced  
25 pressure. To the residue was added water, and the

mixture was extracted with ethyl acetate. The organic  
 layer was washed with water and saturated brine, and  
 dried with anhydrous magnesium sulfate. The solvent was  
 evaporated, and the residue was purified with silica gel  
 5 column chromatography (ethyl acetate/methanol/  
 triethylamine) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(4-  
 propoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-  
 yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-  
 carboxamide (Compound 42) (0.2g) as yellow amorphous.  
 10 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.04 (3H, t,  
 J = 7.3 Hz), 1.34 - 1.48 (2H, m), 1.54 - 1.86 (8H, m), 2.20  
 (3H, s), 2.58 - 2.69 (1H, m), 2.88 (2H, t-like), 3.36 (2H,  
 dt, J = 3.4, 11.0 Hz), 3.52 - 3.58 (5H, m), 3.78 - 3.83 (4H,  
 m), 3.90 (2H, t, J = 10.1 Hz), 4.00 - 4.17 (4H, m), 6.84 -  
 15 7.03 (7H, m), 7.26 - 7.33 (2H, m), 7.45 - 7.61 (7H, m).  
 IR (KBr) v: 2936, 2872, 1651, 1607, 1495 cm<sup>-1</sup>.

#### Working Example 43 (Production of Compound 43)

In THF (5ml) was dissolved 7-[4-(2-  
 butoxyethoxy)phenyl]-1-(3,4-methylenedioxyphenyl)-2,3-  
 20 dihydro-1H-1-benzazepine-4-carboxylic acid (0.25g).  
 Under ice-cooling, to the solution were added oxalyl  
 chloride (0.1ml) and DMF (catalytic amount). The mixture  
 was stirred at room temperature for 1 hour, and the  
 solvent was evaporated under reduced pressure. In THF  
 25 (30ml) was dissolved the residue, and the solution was

added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.13g) and triethylamine (0.35ml) in THF (5ml), under ice-cooling.

The mixture was stirred at room temperature overnight

5 under nitrogen atmosphere and the solvent was evaporated under reduced pressure. To the residue was added water,

and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent

10 was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/

triethylamine) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(3,4-methylenedioxyphenyl)-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-

15 benzazepine-4-carboxamide (Compound 43) (0.28g) as yellow amorphous.

<sup>1</sup>H-NMR ( $\delta$  ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.22 - 1.48 (4H, m), 1.54 - 1.74 (4H, m), 2.20 (3H, s), 2.58 - 2.67 (1H, m), 2.91 (2H, t-like), 3.37 (2H, dt, J = 3.0, 11.2 Hz),  
20 3.52 - 3.59 (4H, m), 3.78 - 3.83 (4H, m), 4.01 - 4.19 (4H, m), 5.95 (2H, s), 6.50 (1H, dd, J = 2.2, 8.4 Hz), 6.61 (1H, d, J = 2.2 Hz), 6.76 (1H, d, J = 8.4 Hz), 6.97 - 7.03 (3H, m), 7.26 - 7.37 (3H, m), 7.46 - 7.59 (7H, m).

IR (KBr)  $\nu$ : 2951, 2872, 1651, 1607, 1514, 1487 cm<sup>-1</sup>.

25 Working Example 44 (Production of Compound 17)

In phosphorus oxychloride (25ml) was dissolved 1-(N-acetylglycyl)-7-[4-(2-butoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.5g). The solution was heated to stir at room temperature for 7 hours and at 50°C for 2 hours, and the solvent was evaporated. To the residue was added sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with basic silica gel column chromatography (ethyl acetate/hexane). The resulting crude crystals were recrystallized from ethyl acetate-hexane to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methyloxazol-5-yl)-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 44) (0.26g) as pale yellow crystals. mp 125 - 128°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.22 - 1.48 (2H, m), 1.54 - 1.76 (6H, m), 2.20 (3H, s), 2.41 (3H, s), 2.55 - 2.70 (1H, m), 2.96 (2H, t-like), 3.36 (2H, dt, J = 2.6, 11.0 Hz), 3.52 - 3.58 (4H, m), 3.72 (2H, t-like), 3.80 (2H, t, J = 4.8 Hz), 4.00 - 4.06 (2H, m), 4.15 (2H, t, J = 4.8 Hz), 6.33 (1H, s), 6.98 (2H, d, J = 8.8 Hz), 7.08 (1H,

d,  $J = 8.4$  Hz), 7.26 - 7.56 (8H, m), 7.76 (1H, s).

IR (KBr)  $\nu$ : 2936, 2870, 1651, 1516, 1495  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{40}\text{H}_{48}\text{N}_4\text{O}_5$ : C, 72.26; H, 7.28; N, 8.43.

Found C, 72.16; H, 7.10; N, 8.51.

5           Working Example 45 (Production of Compound 45)

10           In DMF (20ml) were suspended 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methylthiazol-4-yl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.13g), 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline  
15           dihydrochloride (0.1g) and 1-hydroxybenzotriazole (0.06g). Under ice-cooling, to the suspension were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.15g), triethylamine (0.18ml) and 4-dimethylaminopyridine (catalytic amount), and the mixture  
20           was stirred at room temperature overnight, which was poured into water and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with  
25           silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-diethyl ether-hexane to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methylthiazol-4-yl)-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 45)

(0.087g) as pale yellow crystals.

mp 115 - 123°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.30 - 1.45  
(2H, m), 1.55 - 1.76 (6H, m), 2.21 (3H, s), 2.55 - 2.75 (1H,  
5 m), 2.67 (3H, s), 2.94 (2H, t-like), 3.36 (2H, dt, J = 2.6,  
11.2 Hz), 3.52 - 3.59 (4H, m), 3.81 (2H, t, J = 4.9 Hz),  
4.01 - 4.19 (6H, m), 5.93 (1H, s), 7.00 (2H, d, J = 8.8 Hz),  
7.31 (1H, s), 7.43 - 7.60 (9H, m).

IR (KBr) v: 2932, 2870, 2843, 1659, 1597, 1526, 1518, 1495  
10 cm<sup>-1</sup>.

Working Example 46 (Production of Compound 46)

In DMF (20ml) were suspended 7-[4-(2-  
butoxyethoxy)phenyl]-1-(4-sulfamoylphenyl)-2,3-dihydro-  
1H-1-benzazepine-4-carboxylic acid (0.15g), 4-[N-methyl-  
15 N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline  
dihydrochloride (0.11g) and 1-hydroxybenzotriazole  
(0.06g). Under ice-cooling, to the suspension were added  
1-ethyl-3-(3-dimethylaminopropyl)carbodiimide  
hydrochloride (0.16g), triethylamine (0.2ml) and 4-  
20 dimethylaminopyridine (catalytic amount), and the mixture  
was stirred at room temperature overnight. The solvent  
was evaporated, water was added to the residue, and the  
mixture was extracted with ethyl acetate. The organic  
layer was washed with water and saturated brine, and  
25 dried with anhydrous magnesium sulfate, and the solvent

was evaporated. The residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 7-[4-(2-butoxyethoxy)phenyl]-N-[4-  
 5 [[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-1-(4-sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 46) (0.085g) as yellow crystals.

mp 108 - 111°C.

10 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.2 Hz), 1.33 - 1.48 (2H, m), 1.54 - 1.75 (6H, m), 2.15 (3H, s), 2.57 - 2.67 (1H, m), 2.78 - 2.94 (2H, m), 3.33 (2H, t, J = 10.3 Hz), 3.46 - 3.58 (4H, m), 3.78 - 3.82 (4H, m), 3.97 - 4.02 (2H, m), 4.06 - 4.14 (2H, m), 6.78 (2H, d, J = 9.2 Hz), 6.97 (2H, d, J = 8.8 Hz),  
 15 7.19 - 7.29 (3H, m), 7.36 - 7.63 (9H, m), 8.16 (1H, s).

#### Working Example 47 (Production of Compound 47)

In DMF (25ml) were suspended 7-[4-(2-butoxyethoxy)phenyl]-1-(N,N-dimethyl-4-sulfamoylphenyl)-  
 20 2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.3g), 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline dihydrochloride (0.19g) and 1-hydroxybenzotriazole (0.07g). Under ice-cooling, to the suspension were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide  
 25 hydrochloride (0.15g), triethylamine (0.37ml) and 4-

100183321-121201

dimethylaminopyridine (catalytic amount), and the mixture was stirred at room temperature overnight. The solvent was evaporated, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified with silica gel column (ethyl acetate/methanol/triethylamine) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 7-[4-(2-butoxyethoxy)phenyl]-1-(N,N-dimethyl-4-sulfamoylphenyl)-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 47) (0.12g) as colorless crystals.

mp 94 - 98°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.1 Hz), 1.22 - 1.74 (8H, m), 2.20 (3H, s), 2.55 - 2.70 (1H, m), 2.70 (6H, s), 3.02 (2H, t-like), 3.36 (2H, dt, J = 2.6, 11.0 Hz), 3.53 - 3.60 (4H, m), 3.82 (2H, t, J = 5.0 Hz), 3.85 - 4.14 (4H, m), 4.18 (2H, t, J = 5.0 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.37 - 7.63 (9H, m), 7.70 (1H, d, J = 2.2 Hz).

Working Example 48 (Production of Compound 48)

In THF (7ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(N-methyl-4-sulfamoylphenyl)-2,3-



dihydro-1H-1-benzazepine-4-carboxylic acid (0.4g). Under ice-cooling, to the solution were added oxalyl chloride (0.19ml) and DMF (catalytic amount). The mixture was stirred at room temperature for 1 hour, and the solvent was evaporated under reduced pressure. In THF (25ml) was dissolved the residue, and the solution was added dropwise to a suspension of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline dihydrochloride (0.28g) and triethylamine (0.5ml) in THF (5ml), under ice-cooling.

The mixture was stirred at room temperature under nitrogen atmosphere for 1 hour and the solvent was evaporated under reduced pressure. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with basic silica gel column chromatography (ethyl acetate) to give crude crystals, which were recrystallized from ethyl acetate-hexane to give 7-[4-(2-butoxyethoxy)phenyl]-1-(N-methyl-4-sulfamoylphenyl)-N-[4-[[N-methyl-N-tetrahydro-2H-pyran-4-yl]amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 48) (0.28g) as pale yellow crystals. mp 96 - 99°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.29 - 1.71

(8H, m), 2.17 (3H, s), 2.59 (3H, d,  $J = 4.0$  Hz), 2.60 - 2.70 (1H, m), 2.95 (2H, t-like), 3.35 (2H, dt,  $J = 2.6, 11.4$  Hz), 3.52 - 3.59 (4H, m), 3.79 - 3.88 (4H, m), 3.99 - 4.17 (4H, m), 4.66 (1H, br), 6.86 (2H, d,  $J = 8.8$  Hz), 6.99 (2H, d,  $J = 8.4$  Hz), 7.23 - 7.66 (12H, m), 8.05 (1H, d,  $J = 9.6$  Hz).

IR (KBr)  $\nu$ : 2942, 2853, 1661, 1590, 1495  $\text{cm}^{-1}$ .

#### Reference Example 98

Propionyl chloride (1.0ml) was added dropwise to a suspension of methyl 7-(2-propoxyethoxy)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.2g) and potassium carbonate (2.2g) in DMF (10ml) under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere, and poured into water, which was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 1-propionyl-7-(2-propoxyethoxy)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.2g) as pale yellow oil.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.95 (3H, t,  $J = 7.3$  Hz), 1.05 (3H, t,  $J = 7.3$  Hz), 1.57 - 1.75 (2H, m), 2.09 - 2.20 (1H, m), 2.41 - 2.53 (1H, m), 2.75 - 2.84 (2H, m), 2.88 - 3.10 (1H, m), 3.52 (2H, t,  $J = 6.7$  Hz), 3.80 - 3.83 (5H, m), 4.18 (2H, t,

$J = 4.6 \text{ Hz}$ ), 4.75 - 4.80 (1H, m), 7.03 (2H, d,  $J = 8.8 \text{ Hz}$ ), 7.24 (1H, d,  $J = 8.4 \text{ Hz}$ ), 7.48 - 7.55 (3H, m), 7.65 (1H, d,  $J = 1.8 \text{ Hz}$ ), 7.73 (1H, s).

IR (neat)  $\nu$ : 2948, 2874, 1713, 1661  $\text{cm}^{-1}$ .

5      ~~Reference Example 99~~

In methanol (25ml) and THF (25ml) was dissolved methyl 1-propionyl-7-(2-propoxyethoxy)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.2g), and to the solution was added 1N sodium hydroxide solution (5ml). The mixture  
10 was stirred at room temperature overnight, concentrated. neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-propionyl-  
15 7-(2-propoxyethoxy)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.2g) as colorless crystals.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.95 (3H, t,  $J = 7.3 \text{ Hz}$ ), 1.07 (3H, t,  $J = 7.5 \text{ Hz}$ ), 1.57 - 1.75 (2H, m), 2.12 - 2.22 (1H, m), 2.43 - 2.55 (1H, m), 2.78 - 2.88 (2H, m), 3.00 - 3.10 (1H, m),  
20 3.53 (2H, t,  $J = 6.8 \text{ Hz}$ ), 3.83 (2H, t,  $J = 5.0 \text{ Hz}$ ), 4.19 (2H, t,  $J = 5.0 \text{ Hz}$ ), 4.78 - 4.80 (1H, m), 7.03 (2H, d,  $J = 8.6 \text{ Hz}$ ), 7.26 (1H, d,  $J = 8.2 \text{ Hz}$ ), 7.51 - 7.56 (3H, m), 7.67 (1H, d,  $J = 1.4 \text{ Hz}$ ), 7.83 (1H, s).

IR (KBr)  $\nu$ : 2940, 2876, 1705  $\text{cm}^{-1}$ .

25      Reference Example 100

Amen.  
B42

10018321.121201

In 1,2-dichloroethane (20) were dissolved methyl 7-bromo-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.0g), n-butylaldehyde (1.3ml) and acetic acid (0.41ml), and to the solution was added sodium triacetoxyborohydride

5 (3.8g). The mixture was stirred at room temperature overnight, poured into water, neutralized with sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-bromo-1-butyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.9g) as pale yellow oil.

10 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.96 (3H, t, J = 7.2 Hz), 1.27 - 1.45 (2H, m), 1.56 - 1.72 (2H, m), 2.79 (2H, t, J = 4.2 Hz), 3.19 - 3.31 (4H, m), 3.80 (3H, s), 6.69 (1H, d, J = 8.8 Hz), 7.23 (1H, dd, J = 2.5, 8.8 Hz), 7.42 (1H, d, J = 2.5 Hz), 7.57 (1H, s).

20 Reference Example 101

A mixture of methyl 7-bromo-1-butyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.45g), 4-(2-propoxyethoxy)phenyl borate (0.66g), 1M potassium carbonate solution (4ml), ethanol (4ml) and toluene  
25 (25ml) was stirred under argon atmosphere at room

temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.12g), and the mixture was refluxed overnight under argon atmosphere and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 1-butyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.5g) as pale yellow oil.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.91 - 1.01 (6H, m), 1.30 - 1.45 (2H, m), 1.57 - 1.73 (4H, m), 2.80 (2H, t,  $J = 4.6$  Hz), 3.25 - 3.37 (4H, m), 3.51 (2H, t,  $J = 6.1$  Hz), 3.78 - 3.83 (5H, m), 4.16 (2H, t,  $J = 4.9$  Hz), 6.87 (1H, d,  $J = 8.4$  Hz), 6.97 (2H, d,  $J = 8.8$  Hz), 7.37 - 7.51 (4H, m), 7.76 (1H, s).

IR (neat)  $\nu$ : 2959, 2928, 2870, 1698, 1607, 1501  $\text{cm}^{-1}$ .

#### Reference Example 102

In methanol (25ml) and THF (25ml) was dissolved methyl 1-butyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.5g). To the solution was added 1N sodium hydroxide solution (17ml), and the mixture was heated to stir at  $50^\circ\text{C}$  for 5 hours, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was

washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-butyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.38g) as yellow crystals.

mp 176 - 177°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.91 - 1.02 (6H, m), 1.35 - 1.46 (2H, m), 1.60 - 1.74 (4H, m), 2.84 (2H, t-like), 3.32 - 3.39 (4H, m), 3.52 (2H, t, J = 6.8 Hz), 3.81 (2H, t, J = 5.1 Hz), 4.17 (2H, t, J = 5.1 Hz), 6.88 (1H, d, J = 9.2 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.40 - 7.53 (4H, m), 7.88 (1H, s).

IR (KBr) ν: 2959, 2932, 2872, 1669, 1607, 1501 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>26</sub>H<sub>33</sub>NO<sub>4</sub>: C, 73.73; H, 7.85; N, 3.31. Found C, 73.42; H, 7.86; N, 3.25.

#### Reference Example 103

To cyclopropylamine (50ml) was added dropwise t-butyl 4-bromobutyrate (33.5g) at 40°C. To the mixture was added sodium iodide (22.6g), and the mixture was refluxed overnight. The solvent was evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified by distillation under reduced pressure to give t-butyl N-cyclopropyl-4-aminobutyrate

(12.6g) as colorless oil.

bp 85 - 90°C/5 mm.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.27 - 0.47 (4H, m), 1.45 (9H, s),  
1.69 - 1.84 (2H, m), 2.08 - 2.15 (1H, m), 2.26 (2H, t, J =  
5 7.3 Hz), 2.71 (2H, t, J = 7.3 Hz).

#### Reference Example 104

5-bromo-2-fluorobenzaldehyde (20g), t-butyl N-  
cyclopropyl-4-aminobutyrate (14.5g), sodium carbonate  
(13.8g), water (70ml) and DMSO (70ml) were heated at 80°C  
10 for 5 days and at 110°C for 3 days, which was poured into  
water and extracted with ethyl acetate. The organic  
layer was washed with water and saturated brine and dried  
with anhydrous magnesium sulfate. The solvent was  
evaporated and the residue was purified with silica gel  
15 column chromatography (ethyl acetate/hexane) to give t-  
butyl N-(4-bromo-2-formylphenyl)-N-cyclopropyl-4-  
aminobutyrate (6.4g) as red oil.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.45 - 0.52 (2H, m), 0.72 - 0.78 (2H,  
m), 1.41 (9H, s), 1.88 - 1.98 (2H, m), 2.17 (2H, t, J = 7.1  
20 Hz), 2.66 - 2.73 (1H, m), 3.29 (2H, t, J = 7.5 Hz), 7.13  
(1H, d, J = 8.8 Hz), 7.53 (1H, dd, J = 2.6, 8.8 Hz), 7.84  
(1H, d, J = 2.6 Hz), 10.09 (1H, s).

#### Reference Example 105

In THF(10ml) was dissolved t-butyl N-(4-bromo-2-  
25 formylphenyl)-N-cyclopropyl-4-aminobutyrate (1g). To the

100183321.121201

100183221-121201

solution was added potassium t-butoxide (0.59g), and the mixture was heated at 55°C for 1.5 hours. The solvent was evaporated, which was extracted with water. The aqueous layer was washed with ethyl acetate, and

5 neutralized by addition of 1N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-bromo-1-cyclopropyl-2,3-dihydro-1H-1-

10 benzazepine-4-carboxylic acid (0.44g) as yellow crystals. mp 225 - 230°C (dec.).

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.42 - 0.50 (2H, m), 0.80 - 0.84 (2H, m), 2.60 - 2.80 (3H, m), 3.24 - 3.34 (2H, m), 7.13 (1H, d, J = 8.8 Hz), 7.38 (1H, dd, J = 2.4, 8.8 Hz), 7.45 (1H, s),

15 7.53 (1H, d, J = 2.4 Hz), 12.39 (1H, br).

Anal. Calcd. for C<sub>14</sub>H<sub>14</sub>BrNO<sub>2</sub>: C, 54.56; H, 4.58; N, 4.55. Found C, 54.20; H, 4.60; N, 4.30.

#### Reference Example 106

In THF (15ml) was dissolved 7-bromo-1-cyclopropyl-

20 2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.4g). Under ice-cooling, to the solution were added oxalyl chloride (0.26ml) and DMF (catalytic amount), and the mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure. In

25 THF (30ml) was dissolved the residue, and the solution



was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.34g) and triethylamine (0.9ml) in THF (5ml) under ice-cooling. The mixture was stirred under nitrogen atmosphere at room temperature overnight. The solvent was evaporated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give 7-bromo-1-cyclopropyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.55g) as yellow crystals.

mp 133 - 136°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.50 - 0.58 (2H, m), 0.79 - 0.88 (2H, m), 1.63 - 1.76 (4H, m), 2.20 (3H, s), 2.58 - 2.71 (2H, m), 2.86 (2H, t, J = 8.8 Hz), 3.37 (2H, dt, J = 3.0, 11.4 Hz), 3.46 (2H, t, J = 4.9 Hz), 3.56 (2H, s), 4.01 - 4.07 (2H, m), 7.08 (1H, d, J = 8.8 Hz), 7.14 (1H, s), 7.26 - 7.32 (2H, m), 7.37 (1H, d, J = 2.6 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.57 (1H, s).

Anal. Calcd. for C<sub>27</sub>H<sub>32</sub>BrN<sub>3</sub>O<sub>2</sub>: C, 63.53; H, 6.32; N, 8.23.

Found C, 63.30; H, 6.26; N, 8.15.

## Reference Example 107

In DMF (3ml) was dissolved methyl 7-bromo-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g), and the solution was added dropwise to a suspension of 60% sodium hydride (0.05g) in DMF (1ml) under ice-cooling. The mixture was stirred under nitrogen atmosphere for 10 minutes. Benzyl bromide (0.15ml) was added thereto, and the mixture was heated at 45°C for 4 hours. The mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 1-benzyl-7-bromo-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g) as yellow oil.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 2.75 (2H, t, J = 4.9 Hz), 3.26 (2H, t, J = 4.9 Hz), 3.80 (3H, s), 4.52 (2H, s), 6.67 (1H, d, J = 8.8 Hz), 7.19 (1H, dd, J = 2.4, 8.8 Hz), 7.22 - 7.45 (6H, m), 7.47 (1H, d, J = 2.4 Hz), 7.63 (1H, s).

IR (neat) ν: 1703 cm<sup>-1</sup>.

## Reference Example 108

A mixture of methyl 1-benzyl-7-bromo-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g), 4-(2-propoxyethoxy)phenyl borate (0.24g), 1M potassium carbonate solution (2.5ml), ethanol (2.5ml) and toluene

(25ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.04g), and the mixture was refluxed under argon atmosphere overnight.

5 The mixture was extracted with ethyl acetate, and the organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 1-benzyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.27g) as yellow oil.

<sup>1</sup>H-NMR ( $\delta$  ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.5 Hz), 1.58 - 1.70 (2H, m), 2.77 (2H, t, J = 4.6 Hz), 3.32 (2H, t, J = 4.6 Hz), 15 3.51 (2H, t, J = 6.8 Hz), 3.78 - 3.83 (2H, m), 3.81 (3H, s), 4.07 - 4.18 (2H, m), 4.59 (2H, s), 6.87 (1H, d, J = 8.4 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.26 - 7.41 (6H, m), 7.47 (2H, d, J = 8.8 Hz), 7.56 (1H, d, J = 2.2 Hz), 7.83 (1H, s).

IR (neat)  $\nu$ : 3027, 2874, 1701, 1499 cm<sup>-1</sup>.

20 ~~Reference Example 109~~

~~In methanol (10ml) and THF (10ml) was dissolved methyl 1-benzyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.27g). To the solution was added 1N sodium hydroxide solution (10ml), 25 and the mixture was stirred at room temperature overnight.~~

Amen.  
B43

10018321-121201

and concentrated, which was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-benzyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.16g) as yellow crystals.

mp 139 - 142°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.3 Hz), 1.59 - 1.70 (2H, m), 2.80 (2H, t, J = 4.6 Hz), 3.34 (2H, t, J = 4.6 Hz), 3.52 (2H, t, J = 6.8 Hz), 3.78 - 3.84 (2H, m), 4.14 - 4.19 (2H, m), 4.61 (2H, s), 6.87 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.26 - 7.49 (8H, m), 7.57 (1H, d, J = 2.2 Hz), 7.95 (1H, s).

IR (KBr) v: 2934, 2870, 1674, 1607, 1501 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>29</sub>H<sub>31</sub>NO<sub>4</sub>: C, 76.12; H, 6.83; N, 3.06. Found C, 75.77; H, 6.95; N, 3.15.

#### Reference Example 110

In 1,2-dichloroethane (7ml) were dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.4g) and benzaldehyde (0.43g). To the solution was added sodium triacetoxymethylborohydride (0.43g), and the mixture was stirred under nitrogen atmosphere at room temperature overnight, poured into water, neutralized with sodium hydrogen carbonate solution and

extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give methyl 1-benzyl-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.49g) as oil.

<sup>1</sup>H-NMR ( $\delta$  ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.30 - 1.48 (2H, m), 1.54 - 1.68 (2H, m), 2.77 (2H, t, J = 4.7 Hz), 3.31 (2H, t, J = 4.7 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.78 - 3.82 (5H, m), 4.15 (2H, t, J = 4.8 Hz), 4.59 (2H, s), 6.86 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.26 - 7.68 (7H, m), 7.82 - 7.91 (3H, m).

IR (neat)  $\nu$ : 2934, 2870, 1703, 1607, 1501 cm<sup>-1</sup>.

Reference Example 111

In methanol (25ml) and THF (25ml) was dissolved methyl 1-benzyl-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.49g). To the solution was added 1N sodium hydroxide solution (10ml), and the mixture was heated at 50°C overnight and concentrated, which was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-benzyl-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.47g) as yellow crystals.

Ames  
B4

10018321  
10018321

mp 133 - 138°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.4 Hz), 1.34 - 1.45  
(2H, m), 1.54 - 1.65 (2H, m), 2.80 (2H, br), 3.34 (2H, br),  
3.56 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 5.0 Hz), 4.16  
5 (2H, t, J = 5.0 Hz), 4.61 (2H, s), 6.88 (1H, d, J = 8.8 Hz),  
6.98 (2H, d, J = 8.8 Hz), 7.26 - 7.49 (8H, m), 7.57 (1H, d,  
J = 2.2 Hz), 7.94 (1H, s).

IR (KBr) ν: 2957, 2934, 2867, 1674, 1609, 1501 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>30</sub>H<sub>33</sub>NO<sub>4</sub>: C, 76.41; H, 7.05; N, 2.97. Found  
10 C, 76.06; H, 7.15; N, 2.68.

#### Reference Example 112

In 1,2-dichloroethane (5ml) were dissolved methyl 7-  
[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-  
4-carboxylate (0.3g) and cyclohexanecarboaldehyde (0.43g).  
15 To the solution was added sodium triacetoxymethylborohydride  
(0.43g), and the mixture was stirred under nitrogen  
atmosphere at room temperature for 3.5 hours, poured into  
water, neutralized with sodium hydrogen carbonate  
solution and extracted with ethyl acetate. The organic  
20 layer was washed with water and saturated brine and dried  
with anhydrous magnesium sulfate. The solvent was  
evaporated to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-  
cyclohexylmethyl-2,3-dihydro-1H-1-benzazepine-4-  
carboxylate (0.37g) as pale yellow oil.

25 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.89 - 1.81 (15H, m), 0.93 (3H, t, J =

7.3 Hz), 2.81 (2H, t, J = 4.2 Hz), 3.19 (2H, d, J = 6.6 Hz),  
3.29 (2H, t, J = 4.8 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.78 -  
3.82 (5H, m), 4.15 (2H, t, J = 4.9 Hz), 6.87 (1H, d, J =  
8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.36 - 7.51 (4H, m),  
5 7.76 (1H, s).

IR (neat)  $\nu$ : 2930, 2849, 1699, 1607, 1499  $\text{cm}^{-1}$ .

#### Reference Example 113

In methanol (25ml) and THF (25ml) was dissolved  
methyl 7-[4-(2-butoxyethoxy)phenyl]-1-cyclohexylmethyl-  
10 2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.37g). To  
the solution was added 1N sodium hydroxide solution  
(7.5ml), and the mixture was stirred at room temperature  
overnight and concentrated, which was neutralized with 1N  
hydrochloric acid and extracted with ethyl acetate. The  
15 organic layer was washed with water and saturated brine  
and dried with anhydrous magnesium sulfate. The solvent  
was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-  
cyclohexylmethyl-2,3-dihydro-1H-1-benzazepine-4-  
carboxylic acid (0.32g) as yellow crystals.

20 mp 124 - 125°C.

$^1\text{H}$ -NMR ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.90 - 1.85 (15H, m), 0.93 (3H, t, J =  
7.2 Hz), 2.83 (2H, t-like), 3.22 (2H, d, J = 6.6 Hz), 3.32  
(2H, t-like), 3.56 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J =  
5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.89 (1H, d, J = 8.8 Hz),  
25 6.98 (2H, d, J = 8.8 Hz), 7.39 - 7.53 (4H, m), 7.88 (1H, s).

10018321-121201

IR (KBr)  $\nu$ : 2926, 1674, 1607, 1499  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{30}\text{H}_{39}\text{NO}_4$ : C, 75.44; H, 8.23; N, 2.93. Found C, 75.46; H, 8.23; N, 2.96.

#### Reference Example 114

5        In 1,2-dichloroethane (7ml) were dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.4g) and cyclopropanecarboaldehyde (0.3g). To the solution was added sodium triacetoxymethylborohydride (0.43g), and the mixture was stirred under nitrogen  
10        atmosphere at room temperature overnight, poured into water, neutralized with sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was  
15        evaporated to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-cyclopropylmethyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.45g) as yellow oil.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.24 - 0.32 (2H, m), 0.58 - 0.67 (2H, m), 0.93 (3H, t,  $J = 7.3$  Hz), 1.08 - 1.15 (1H, m), 1.34 -  
20        1.49 (2H, m), 1.55 - 1.68 (2H, m), 2.86 (2H, t,  $J = 4.4$  Hz), 3.23 (2H, d,  $J = 6.6$  Hz), 3.39 (2H, t,  $J = 4.7$  Hz), 3.55 (2H, t,  $J = 6.6$  Hz), 3.73 - 3.83 (5H, m), 4.11 - 4.18 (2H, m), 6.92 - 7.01 (3H, m), 7.38 - 7.53 (4H, m), 7.77 (1H, s).

IR (neat)  $\nu$ : 2953, 2930, 2870, 1699, 1607, 1499  $\text{cm}^{-1}$ .

25        Reference Example 115



In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-cyclopropylmethyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.45g). To the solution was added 1N sodium hydroxide solution (10ml), and the mixture was stirred at room temperature overnight and concentrated, which was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-cyclopropylmethyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.42g) as yellow crystals.

mp 152 - 155°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.25 - 0.33 (2H, m), 0.59 - 0.68 (2H, m), 0.93 (3H, t, J = 7.3 Hz), 1.05 - 1.20 (1H, m), 1.30 - 1.49 (2H, m), 1.55 - 1.69 (2H, m), 2.87 (2H, t, J = 4.6 Hz), 3.25 (2H, d, J = 6.4 Hz), 3.42 (2H, t, J = 4.6 Hz), 3.56 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.93 - 7.00 (3H, m), 7.40 - 7.54 (4H, m), 7.89 (1H, s).

IR (KBr) v: 2959, 2936, 2868, 1669, 1607, 1501 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>27</sub>H<sub>33</sub>NO<sub>4</sub>: C, 74.45; H, 7.64; N, 3.22. Found C, 74.27; H, 7.45; N, 3.21.

#### Reference Example 116

In 1,2-dichloroethane (5ml) were dissolved methyl 7-

10018321-121201

[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g) and cyclopropanecarboaldehyde (0.22g). To the solution was added sodium triacetoxymethylborohydride (0.33g), and the mixture was stirred under nitrogen atmosphere at room temperature for 4 hours, poured into water, neutralized with sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give methyl 1-cyclopropylmethy-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.34g) as yellow oil.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.24 - 0.32 (2H, m), 0.58 - 0.67 (2H, m), 0.94 (3H, t, J = 7.5 Hz), 1.05 - 1.15 (1H, m), 1.60 - 1.74 (2H, m), 2.85 (2H, t, J = 4.6 Hz), 3.23 (2H, d, J = 6.6 Hz), 3.39 (2H, t, J = 4.6 Hz), 3.51 (2H, t, J = 6.7 Hz), 3.79 - 3.84 (5H, m), 4.16 (2H, t, J = 5.0 Hz), 6.91 - 7.01 (3H, m), 7.38 - 7.52 (4H, m), 7.77 (1H, s).

IR (neat) v: 2936, 2872, 1699, 1607, 1499 cm<sup>-1</sup>.

Reference Example 117

In methanol (25ml) and THF (25ml) was dissolved methyl 1-cyclopropylmethy-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.34g). To the solution was added 1N sodium hydroxide solution

(7.5ml), and the mixture was stirred at room temperature overnight, heated at 50°C for 1 hour, concentrated, which was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with  
 5 water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-cyclopropylmethyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.30g) as yellow crystals.

10 mp 154 - 156°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.25 - 0.33 (2H, m), 0.59 - 0.68 (2H, m), 0.95 (3H, t, J = 7.3 Hz), 1.05 - 1.18 (1H, m), 1.56 - 1.74 (2H, m), 2.87 (2H, t, J = 4.8 Hz), 3.25 (2H, d, J = 6.2 Hz), 3.42 (2H, t, J = 4.8 Hz), 3.51 (2H, t, J = 6.8 Hz),  
 15 3.81 (2H, t, J = 4.9 Hz), 4.17 (2H, t, J = 4.9 Hz), 6.93 - 7.00 (3H, m), 7.40 - 7.53 (4H, m), 7.88 (1H, s).

IR (KBr) v: 2963, 1669, 1518 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>26</sub>H<sub>31</sub>NO<sub>4</sub>: C, 74.08; H, 7.41; N, 3.32. Found C, 74.03; H, 7.53; N, 3.27.

20 Reference Example 118

In 1,2-dichloroethane (7ml) were dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.4g) and cyclobutanecarboaldehyde (0.5g). To the solution was added sodium triacetoxymethylborohydride  
 25 (0.43g), and the mixture was stirred under nitrogen

atmosphere at room temperature for 4 hours, poured into water, neutralized with sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-cyclobutylmethyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.47g) as yellow oil.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.34 - 1.45 (2H, m), 1.54 - 2.13 (8H, m), 2.70 - 2.81 (3H, m), 3.26 (2H, t, J = 4.8 Hz), 3.38 (2H, d, J = 7.4 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.78 - 3.83 (5H, m), 4.16 (2H, t, J = 4.9 Hz), 6.87 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.37 - 7.51 (4H, m), 7.75 (1H, s)

#### Reference Example 119

In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-cyclobutylmethyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.47g). To the solution was added 1N sodium hydroxide solution (10ml), and the mixture was heated at 50°C overnight, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-cyclobutylmethyl-

2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.40g) as yellow crystals.

mp 110 - 112°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.30 - 2.00  
5 (8H, m), 2.00 - 2.15 (2H, m), 2.71 - 2.80 (3H, m), 3.29 (2H, t, J = 4.8 Hz), 3.39 (2H, d, J = 7.0 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.88 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.39 - 7.51 (4H, m), 7.85 (1H, s).

10 Anal. Calcd. for C<sub>28</sub>H<sub>35</sub>NO<sub>4</sub>: C, 74.80; H, 7.85; N, 3.12. Found C, 74.51; H, 7.92; N, 2.98.

#### Reference Example 120

In dichloromethane (15ml) were dissolved methyl 7-bromo-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.5g)  
15 and copper pivalate (0.05g). To the solution was added triphenylbismuth diacetate (1.1g), and the mixture was stirred at room temperature overnight, poured into water, stirred, neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was  
20 washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-bromo-1-phenyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate  
25 (0.27g) as yellow crystals.

10018331-121201

mp 104 - 106°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 2.82 (2H, t, J = 4.4 Hz), 3.76 (2H, t, J = 4.4 Hz), 3.78 (3H, s), 6.90 - 7.00 (4H, m), 7.22 - 7.30 (3H, m), 7.58 (1H, d, J = 2.2 Hz), 7.62 (1H, s).

5 IR (KBr) v: 2949, 1705 cm<sup>-1</sup>.

Anal. calcd for C<sub>18</sub>H<sub>16</sub>BrNO<sub>2</sub>: C, 60.35; H, 4.50; N, 3.91.  
Found C, 60.16; H, 4.28; N, 3.85.

#### Reference Example 121

10 A mixture of methyl 7-bromo-1-phenyl-2,3-dihydro-1H-  
1-benzazepine-4-carboxylate (0.27g), 4-(2-propoxyethoxy)phenyl borate (0.23g), 1M potassium carbonate solution (3ml), ethanol (3ml) and toluene (25ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added  
15 tetrakis(triphenylphosphine)palladium (0.04g), and the mixture was refluxed under argon atmosphere overnight, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated  
20 under reduced pressure and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 1-phenyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.26g) as yellow crystals.  
25 mp 117 - 119°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.95 (3H, t, J = 7.5 Hz), 1.57 - 1.71 (2H, m), 2.85 (2H, t, J = 4.6 Hz), 3.52 (2H, t, J = 6.8 Hz), 3.79 (3H, s), 3.79 - 3.84 (4H, m), 4.18 (2H, t, J = 5.0 Hz), 6.87 - 7.03 (5H, m), 7.16 - 7.30 (3H, m), 7.40 (1H, dd, J = 2.2, 8.4 Hz), 7.51 (2H, d, J = 8.8 Hz), 7.64 (1H, d, J = 2.2 Hz), 7.80 (1H, s).

IR (KBr) v: 1705, 1493 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>29</sub>H<sub>31</sub>NO<sub>4</sub>: C, 76.12; H, 6.83; N, 3.06. Found C, 75.81; H, 6.75; N, 2.77.

10 Reference Example 122

In methanol (25ml) and THF (25ml) was dissolved methyl 1-phenyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.23g). To the solution was added 1N sodium hydroxide solution (10ml), and the mixture was heated at 50°C overnight, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-phenyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.23g) as yellow crystals.

mp 135 - 139°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.95 (3H, t, J = 7.5 Hz), 1.60 - 1.71 (2H, m), 2.86 (2H, t-like), 3.52 (2H, t, J = 6.7 Hz), 3.80

- 3.85 (4H, m), 4.18 (2H, t,  $J = 4.8$  Hz), 6.90 - 7.04 (5H, m), 7.17 (1H, d,  $J = 8.5$  Hz), 7.23 - 7.31 (2H, m), 7.40 (1H, dd,  $J = 2.2, 8.5$  Hz), 7.51 (2H, d,  $J = 8.8$  Hz), 7.65 (1H, d,  $J = 2.2$  Hz), 7.90 (1H, s).

- 5 IR (KBr)  $\nu$ : 2963, 2936, 2872, 1674, 1609, 1593, 1493  $\text{cm}^{-1}$ .  
 Anal. Calcd. for  $\text{C}_{28}\text{H}_{29}\text{NO}_4$ : C, 75.82; H, 6.59; N, 3.16. Found  
 C, 75.43; H, 6.37; N, 3.10.

#### Reference Example 123

- In dichloromethane (10ml) were dissolved methyl 7-  
 10 [4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-  
 4-carboxylate (0.5g) and copper pivalate (0.07g). To the  
 solution was added triphenylbismuth diacetate (0.78g),  
 and the mixture was stirred at room temperature overnight,  
 poured into 3N hydrochloric acid, stirred, neutralized  
 15 with 1N sodium hydroxide solution and extracted with  
 ethyl acetate. The organic layer was washed with water  
 and saturated brine and dried with anhydrous magnesium  
 sulfate. The solvent was evaporated and the residue was  
 purified with silica gel column chromatography (ethyl  
 20 acetate/hexane) to give methyl 7-[4-(2-  
 butoxyethoxy)phenyl]-1-phenyl-2,3-dihydro-1H-1-  
 benzazepine-4-carboxylate (0.42g) as yellow crystals.  
 mp 80 - 82°C.

- $^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.94 (3H, t,  $J = 7.1$  Hz), 1.31 - 1.49  
 25 (2H, m), 1.56 - 1.69 (2H, m), 2.85 (2H, t,  $J = 4.4$  Hz),



3.56 (2H, t,  $J = 6.6$  Hz), 3.79 - 3.84 (7H, m), 4.17 (2H, t,  $J = 4.9$  Hz), 6.87 - 7.02 (5H, m), 7.16 - 7.30 (3H, m), 7.40 (1H, dd,  $J = 2.2, 8.8$  Hz), 7.51 (2H, d,  $J = 8.4$  Hz), 7.64 (1H, d,  $J = 2.2$  Hz), 7.80 (1H, s).

5 IR (KBr)  $\nu$ : 2955, 2868, 1705, 1593, 1495  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{30}\text{H}_{33}\text{NO}_4$ : C, 76.41; H, 7.05; N, 2.97. Found C, 76.30; H, 7.17; N, 2.90.

#### Reference Example 124

10 In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-phenyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.37g). To the solution was added 1N sodium hydroxide solution (7.5ml), and the mixture was stirred at room temperature overnight, concentrated, neutralized with 1N hydrochloric acid and  
15 extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-phenyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.27g) as  
20 yellow crystals.  
mp 129 - 131°C.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.94 (3H, t,  $J = 7.2$  Hz), 1.34 - 1.49 (2H, m), 1.55 - 1.69 (2H, m), 2.86 (2H, t,  $J = 4.4$  Hz), 3.56 (2H, t,  $J = 6.6$  Hz), 3.79 - 3.84 (4H, m), 4.17 (2H, t,  $J = 4.8$  Hz), 6.90 - 7.04 (5H, m), 7.17 (1H, d,  $J = 8.6$  Hz),  
25

7.23 - 7.31 (2H, m), 7.40 (1H, dd,  $J = 2.2, 8.6$  Hz), 7.50 (2H, d,  $J = 7.2$  Hz), 7.64 (1H, d,  $J = 1.8$  Hz), 7.90 (1H, s). IR (KBr)  $\nu$ : 2957, 2870, 1674, 1609, 1593, 1493  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{29}\text{H}_{31}\text{NO}_4$ : C, 76.12; H, 6.83; N, 3.06. Found  
5 C, 76.18; H, 6.85; N, 3.21.

#### Reference Example 125

In dichloromethane (7ml) were dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.25g) and copper pivalate (0.04g). To the  
10 solution was added tri(3-methoxyphenyl)bismuth diacetate (1.5g), and the mixture was stirred at room temperature overnight, poured into 3N hydrochloric acid, stirred, neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was  
15 washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(3-methoxyphenyl)-2,3-  
20 dihydro-1H-1-benzazepine-4-carboxylate (0.16g) as yellow oil.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.94 (3H, t,  $J = 7.2$  Hz), 1.34 - 1.45 (2H, m), 1.55 - 1.65 (2H, m), 2.86 (2H, t,  $J = 4.8$  Hz), 3.56 (2H, t,  $J = 6.6$  Hz), 3.75 (3H, s), 3.79 (3H, s), 3.79  
25 - 3.84 (4H, m), 4.17 (2H, t,  $J = 4.9$  Hz), 6.42 - 6.60 (3H,

m), 7.00 (2H, d,  $J = 8.8$  Hz), 7.11 - 7.26 (2H, m), 7.41 (1H, dd,  $J = 2.2, 8.4$  Hz), 7.51 (2H, d,  $J = 8.8$  Hz), 7.64 (1H, d,  $J = 2.2$  Hz), 7.78 (1H, s).

IR (neat)  $\nu$ : 2955, 2932, 2870, 1705  $\text{cm}^{-1}$ .

5           Reference Example 126

In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(3-methoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.16g). To the solution was added 1N sodium hydroxide solution  
10 (2.8ml), and the mixture was heated at 50°C overnight, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated  
15 to give 7-[4-(2-butoxyethoxy)phenyl]-1-(3-methoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.16g) as yellow crystals.

mp 154 - 156°C.

$^1\text{H}$ -NMR ( $\delta$  ppm,  $\text{CDCl}_3$ ) 0.94 (3H, t,  $J = 7.4$  Hz), 1.34 - 1.45  
20 (2H, m), 1.55 - 1.65 (2H, m), 2.87 (2H, t-like), 3.56 (2H, t,  $J = 6.6$  Hz), 3.76 (3H, s), 3.79 - 3.84 (4H, m), 4.17 (2H, t,  $J = 4.8$  Hz), 6.45 - 6.61 (3H, m), 7.00 (2H, d,  $J = 8.8$  Hz), 7.13 - 7.24 (2H, m), 7.42 (1H, dd,  $J = 2.2, 8.4$  Hz), 7.51 (2H, d,  $J = 8.8$  Hz), 7.64 (1H, d,  $J = 2.2$  Hz), 7.88  
25 (1H, s).

Anal. Calcd. for  $C_{30}H_{33}NO_5$ : C, 73.90; H, 6.82; N, 2.87. Found C, 73.73; H, 6.72; N, 2.83.

Reference Example 127

In dichloromethane (10ml) were dissolved methyl 7-  
5 [4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g) and copper pivalate (0.06g). To the solution was added tri(4-methoxyphenyl)bismuth diacetate (1.5g), and the mixture was stirred at room temperature overnight, poured into 3N hydrochloric acid, stirred,  
10 neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column  
15 chromatography (ethyl acetate/hexane) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(4-methoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.38g) as yellow oil.

$^1H$ -NMR ( $\delta$  ppm,  $CDCl_3$ ) 0.93 (3H, t,  $J = 7.2$  Hz), 1.30 - 1.45  
20 (2H, m), 1.55 - 1.65 (2H, m), 2.82 (2H, t,  $J = 4.4$  Hz), 3.56 (2H, t,  $J = 6.6$  Hz), 3.72 - 3.83 (10H, m), 4.16 (2H, t,  $J = 4.4$  Hz), 6.85 - 6.91 (3H, m), 6.96 - 7.04 (4H, m), 7.30 (1H, dd,  $J = 2.2, 8.4$  Hz), 7.48 (2H, d,  $J = 8.8$  Hz), 7.59 (1H, d,  $J = 2.2$  Hz), 7.82 (1H, s).

25 IR (neat) v: 2955, 1705, 1609, 1508, 1491  $cm^{-1}$ .

## Reference Example 128

In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(4-methoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.38g). To  
5 the solution was added 1N sodium hydroxide solution (8ml), and the mixture was heated at 50°C overnight, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with  
10 anhydrous magnesium sulfate. The solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-(4-methoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid(0.27g) as yellow crystals.

mp 164 - 166°C.

15 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.1 Hz), 1.34 - 1.49 (2H, m), 1.54 - 1.68 (2H, m), 2.83 (2H, t-like), 3.55 (2H, t, J = 6.0 Hz), 3.74 - 3.83 (7H, m), 4.16 (2H, t, J = 4.9 Hz), 6.85 - 7.06 (7H, m), 7.31 (1H, dd, J = 2.2, 8.4 Hz), 7.47 (2H, d, J = 8.8 Hz), 7.59 (1H, d, J = 2.2 Hz), 7.92  
20 (1H, s).

IR (KBr) v: 2957, 2928, 2868, 1674, 1609, 1508, 1493 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>30</sub>H<sub>33</sub>NO<sub>5</sub>: C, 73.90; H, 6.82; N, 2.87. Found C, 73.87; H, 6.89; N, 2.70.

## Reference Example 129

25 In dichloromethane (7ml) were dissolved methyl 7-[4-

(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.2g) and copper pivalate (0.04g). To the solution was added tri(4-propoxyphenyl)bismuth diacetate (1.1g), and the mixture was stirred at room temperature overnight, poured into 3N hydrochloric acid, stirred, neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.25g) as yellow oil.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.04 (3H, t, J = 7.5 Hz), 1.34 - 1.45 (2H, m), 1.54 - 1.68 (2H, m), 1.75 - 1.86 (2H, m), 2.81 (2H, t, J = 4.4 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.71 - 3.83 (7H, m), 3.90 (2H, t, J = 6.6 Hz), 4.14 - 4.18 (2H, m), 6.84 - 6.90 (3H, m), 6.96 - 7.02 (4H, m), 7.29 (1H, dd, J = 2.2, 8.4 Hz), 7.48 (2H, d, J = 6.6 Hz), 7.58 (1H, d, J = 2.2 Hz), 7.82 (1H, s).

IR (neat) ν: 2957, 2934, 2870, 1705, 1622, 1609, 1507, 1489 cm<sup>-1</sup>.

## Reference Example 130

In methanol (50ml) and THF (50ml) was dissolved

methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(4-propoxyphenyl)-  
 2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.25g). To  
 the solution was added 1N sodium hydroxide solution (5ml),  
 and the mixture was heated at 50°C overnight,  
 5 concentrated, neutralized with 1N hydrochloric acid and  
 extracted with ethyl acetate. The organic layer was  
 washed with water and saturated brine and dried with  
 anhydrous magnesium sulfate. The solvent was evaporated  
 to give 7-[4-(2-butoxyethoxy)phenyl]-1-(4-propoxyphenyl)-  
 10 2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.21g) as  
 yellow crystals.

mp 182 - 185°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.1 Hz), 1.04 (3H, t,  
 J = 7.6 Hz), 1.30 - 1.49 (2H, m), 1.54 - 1.68 (2H, m), 1.76  
 15 - 1.86 (2H, m), 2.83 (2H, t-like), 3.55 (2H, t, J = 6.6 Hz),  
 3.76 (2H, t-like), 3.80 (2H, t, J = 5.0 Hz), 3.91 (2H, t, J  
 = 6.6 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.84 - 7.05 (7H, m),  
 7.30 (1H, dd, J = 2.2, 8.6 Hz), 7.47 (2H, d, J = 8.8 Hz),  
 7.58 (1H, d, J = 2.2 Hz), 7.92 (1H, s).

20 IR (KBr) v: 2959, 2934, 2872, 1669, 1609, 1508, 1493 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>32</sub>H<sub>37</sub>NO<sub>5</sub>: C, 74.54; H, 7.23; N, 2.72. Found  
 C, 74.19; H, 7.32; N, 2.87.

#### Reference Example 131

In dichloromethane (7ml) were dissolved methyl 7-[4-  
 25 (2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-

carboxylate (0.25g) and copper pivalate (0.05g). To the solution was added tri(3,4-methylenedioxyphenyl)bismuth diacetate (1.3g), and the mixture was stirred at room temperature overnight, poured into 3N hydrochloric acid, stirred, neutralized with 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(3,4-methylenedioxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g) as yellow oil.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.2 Hz), 1.30 - 1.49 (2H, m), 1.55 - 1.68 (2H, m), 2.82 (2H, t, J = 4.6 Hz), 3.56 (2H, t, J = 6.6 Hz), 3.73 (2H, t, J = 4.9 Hz), 3.79 - 3.84 (5H, m), 4.17 (2H, t, J = 4.9 Hz), 5.94 (2H, s), 6.49 (1H, dd, J = 2.2, 8.4 Hz), 6.60 (1H, d, J = 2.2 Hz), 6.75 (1H, d, J = 8.4 Hz), 6.94 - 7.02 (3H, m), 7.33 (1H, dd, J = 2.2, 8.4 Hz), 7.48 (2H, d, J = 8.8 Hz), 7.59 (1H, d, J = 2.2 Hz), 7.80 (1H, s).

IR (neat) ν: 2955, 2932, 2870, 1703, 1609, 1485 cm<sup>-1</sup>.

#### Reference Example 132

In methanol (25ml) and THF (25ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(3,4-



methylenedioxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.3g). To the solution was added 1N sodium hydroxide solution (6ml), and the mixture was refluxed for 2 hours, concentrated, neutralized with 1N

5 hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-(3,4-methylenedioxyphenyl)-2,3-dihydro-1H-1-benzazepine-

10 4-carboxylic acid (0.26g) as yellow crystals.  
mp 145 - 148°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.3 Hz), 1.30 - 1.49 (2H, m), 1.55 - 1.68 (2H, m), 2.84 (2H, t, J = 5.2 Hz), 3.56 (2H, t, J = 6.6 Hz), 3.74 (2H, t, J = 5.2 Hz), 3.81

15 (2H, t, J = 5.0 Hz), 4.17 (2H, t, J = 5.0 Hz), 5.95 (2H, s), 6.52 (1H, dd, J = 2.2, 8.4 Hz), 6.62 (1H, d, J = 2.2 Hz), 6.76 (1H, d, J = 8.4 Hz), 6.92 - 7.01 (3H, m), 7.34 (1H, dd, J = 2.2, 8.4 Hz), 7.48 (2H, d, J = 8.8 Hz), 7.59 (1H, d, J = 2.2 Hz), 7.91 (1H, s).

20 IR (KBr) ν: 2932, 2867, 1678, 1609, 1486 cm<sup>-1</sup>.  
Anal. Calcd. for C<sub>30</sub>H<sub>31</sub>NO<sub>6</sub>: C, 71.84; H, 6.23; N, 2.79. Found C, 71.61; H, 6.19; N, 2.62.

## Reference Example 133

In THF (25ml) were dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-

25

carboxylate (1g) and pyridine (2ml). Under ice-cooling, to the solution was added dropwise chloroacetyl chloride (1ml). The mixture was stirred under nitrogen atmosphere at room temperature for 1 hour, and the solvent was  
5 evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel  
10 column chromatography (ethyl acetate/hexane) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-chloroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.1g) as pale yellow oil.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.2 Hz), 1.30 - 1.69  
15 (4H, m), 2.78 - 3.13 (3H, m), 3.56 (2H, t, J = 6.6 Hz), 3.80 - 3.84 (5H, m), 3.93 (1H, d, J = 12.8 Hz), 4.11 - 4.20 (3H, m), 4.76 - 7.84 (1H, m), 7.03 (2H, d, J = 8.8 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.50 - 7.58 (3H, m), 7.68 (1H, d, J = 1.8 Hz), 7.74 (1H, s).

20 Reference Example 134

In DMF (30ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-chloroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.1g). To the solution was added sodium azide (0.23g), and the mixture was heated at  
25 65°C for 1 hour, poured into water and extracted with

100183321.121201  
T02121T T228T001

ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give pale yellow oil (0.8g), which was dissolved in THF (50ml). To the solution were added triphenylphosphine (1.1g) and water (catalytic amount), and the mixture was heated at 50°C for 1.5 hours. The solvent was evaporated and, to the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give pale yellow oil (0.7g), which was dissolved in THF (15ml). To the solution were added pyridine (0.7ml) and acetic anhydride (0.25ml), and the mixture was stirred under nitrogen atmosphere at room temperature overnight. The solvent was evaporated and, to the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give methyl 1-(N-acetylglycyl)-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-

carboxylate (0.67g) as colorless crystals.

mp 130 - 134°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.3 Hz), 1.26 - 1.69 (4H, m), 2.01 (3H, s), 2.76 - 3.12 (3H, m), 3.51 - 3.62 (3H, m), 3.78 - 3.83 (5H, m), 4.16 (2H, t, J = 4.9 Hz), 4.33 (1H, dd, J = 4.0, 18.0 Hz), 4.73 - 4.80 (1H, m), 6.42 (1H, br), 7.03 (2H, d, J = 8.8 Hz), 7.28 (1H, d, J = 7.8 Hz), 7.49 - 7.56 (3H, m), 7.65 (1H, d, J = 2.2 Hz), 7.72 (1H, s).

IR (KBr) v: 3316, 2951, 2934, 2870, 1713, 1661 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>28</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>: C, 68.00; H, 6.93; N, 5.66. Found C, 67.84; H, 6.74; N, 5.61.

#### Reference Example 135

In methanol (50ml) was dissolved methyl 1-(N-acetylglycyl)-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.2g). To the solution was added 1N sodium hydroxide solution (13ml), and the mixture was stirred at room temperature overnight, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-(N-acetylglycyl)-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (1.2g) as colorless crystals.

mp 196 - 201°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.3 Hz), 1.26 - 1.69 (4H, m), 2.02 (3H, s), 2.78 - 3.15 (3H, m), 3.53 - 3.62 (3H, m), 3.82 (2H, t, J = 4.9 Hz), 4.19 (2H, t, J = 4.9 Hz), 4.36 (1H, dd, J = 4.0, 18.0 Hz), 4.75 - 4.82 (1H, m), 6.53 (1H, br), 7.03 (2H, d, J = 8.8 Hz), 7.31 (1H, d, J = 8.0 Hz), 7.50 - 7.58 (3H, m), 7.67 (1H, d, J = 2.2 Hz), 7.81 (1H, s).

IR (KBr) ν: 2951, 2872, 1669 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>: C, 66.86; H, 6.75; N, 5.78.

Found C, 66.65; H, 6.73; N, 5.97.

#### Reference Example 136

In DMF (20ml) were suspended 1-(N-acetylglycyl)-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.85g), 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline dihydrochloride (0.52g) and 1-hydroxybenzotriazole (0.3g). Under ice-cooling, to the suspension were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1g), triethylamine (1.7ml) and 4-dimethylaminopyridine (catalytic amount), and the mixture was stirred at room temperature overnight. The solvent was evaporated and, to the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated

10018321-121201

and the residue was purified with basic silica gel column chromatography (ethyl acetate/methanol/triethylamine) to give 1-(N-acetylglycyl)-7-[4-(2-butoxyethoxy)phenyl]-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (1.1g) as pale yellow amorphous.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.93 (3H, t, J = 7.4 Hz), 1.25 - 1.75 (8H, m), 2.05 (3H, s), 2.19 (3H, s), 2.55 - 2.70 (1H, m), 2.86 - 3.14 (3H, m), 3.37 (2H, dt, J = 2.6, 11.0 Hz), 3.53 - 3.71 (5H, m), 3.82 (2H, t, J = 5.0 Hz), 4.01 - 4.07 (2H, m), 4.11 - 4.28 (3H, m), 4.75 - 4.81 (1H, m), 6.49 (1H, br), 7.02 (2H, d, J = 8.4 Hz), 7.24 - 7.33 (4H, m), 7.43 - 7.61 (6H, m), 8.09 (1H, s).

#### Reference Example 137

In toluene (25ml) were suspended methyl 7-[4-(2-butoxyethoxy)phenyl]-1-chloroacetyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.75g) and thioacetamide (0.36g). The suspension was heated at 90°C for 1 hour and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methylthiazol-4-yl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.17g) as yellow

oil.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.2 Hz), 1.26 - 1.65 (4H, m), 2.67 (3H, s), 2.86 (2H, t, J = 5.3 Hz), 3.56 (2H, t, J = 6.6 Hz), 3.80 (3H, s), 3.81 (2H, t, J = 4.9 Hz),  
5 3.95 (2H, t, J = 5.3 Hz), 4.17 (2H, t, J = 4.9 Hz), 5.92 (1H, s), 7.00 (2H, d, J = 8.8 Hz), 7.43 (2H, s), 7.51 (2H, d, J = 8.8 Hz), 7.62 (1H, s), 7.77 (1H, s).

Reference Example 138

In dichloromethane (15ml) was dissolved methyl 7-bromo-1-phenyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate  
10 (0.68g). Under ice-cooling, to the solution was added dropwise chlorosulfonic acid (0.32ml). The mixture was stirred at room temperature for 30 minutes and, to the mixture was additionally added chlorosulfonic acid  
15 (0.2ml), and the mixture was stirred at room temperature for 10 minutes. The reaction solution was added dropwise to aqueous ammonia (10ml) under ice-cooling, and the mixture was stirred for 30 minutes. The solvent was evaporated and, to the residue was added hot ethyl  
20 acetate. The insolubles were filtered and the solvent in the filtrate was evaporated. The precipitated methyl 7-bromo-1-(4-sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.33g) was collected by filtration and washed with ethyl acetate-hexane to give the carboxylate  
25 as yellow crystals.

mp 200 - 203°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 2.89 (2H, t, J = 5.5 Hz), 3.78 (3H, s),  
3.84 (2H, t, J = 5.5 Hz), 4.65 (2H, s), 6.87 (2H, d, J =  
9.2 Hz), 7.18 (1H, d, J = 8.4 Hz), 7.43 (1H, dd, J = 2.2,  
5 8.4 Hz), 7.60 (1H, s), 7.68 (1H, d, J = 2.2 Hz), 7.73 (2H,  
d, J = 9.2 Hz).

IR (KBr) v: 1713 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>18</sub>H<sub>17</sub>BrN<sub>2</sub>O<sub>4</sub>S: C, 49.44; H, 3.92; N, 6.41.

Found C, 49.30; H, 4.20; N, 6.04.

10       Reference Example 139

A mixture of methyl 7-bromo-1-(4-sulfamoylphenyl)-  
2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.31g), 4-(2-  
butoxyethoxy)phenyl borate (0.22g), 1M potassium  
carbonate solution (3ml), ethanol (5ml) and toluene  
15 (50ml) was stirred under argon atmosphere at room  
temperature for 30 minutes. To the mixture was added  
tetrakis(triphenylphosphine)palladium (0.04g), and the  
mixture was refluxed under argon atmosphere for 3 hours  
and extracted with ethyl acetate. The organic layer was  
20 washed with water and saturated brine and dried with  
anhydrous magnesium sulfate. The solvent was evaporated  
under reduced pressure and the residue was purified with  
silica gel column chromatography (ethyl acetate/hexane)  
to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(4-  
25 sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-



carboxylate (0.34g) as yellow crystals.

mp 163 - 165°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.3 Hz), 1.35 - 1.46 (2H, m), 1.56 - 1.66 (2H, m), 2.92 (2H, t, J = 5.0 Hz),  
5 3.57 (2H, t, J = 6.6 Hz), 3.79 (3H, s), 3.79 - 3.92 (4H, m),  
4.18 (2H, t, J = 4.8 Hz), 4.73 (2H, s), 6.91 (2H, d, J =  
9.2 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.34 (1H, d, J = 8.2 Hz),  
7.50 - 7.56 (3H, m), 7.71 - 7.77 (4H, m).

IR (KBr) v: 2957, 2934, 2870, 1705, 1590, 1493 cm<sup>-1</sup>.

10 Anal. Calcd. for C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S · 0.25H<sub>2</sub>O: C, 65.43; H, 6.22; N,  
5.09. Found C, 65.04; H, 6.35; N, 4.91.

#### Reference Example 140

In methanol (50ml) and THF (15ml) was dissolved  
methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(4-  
15 sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-  
carboxylate (0.34g). To the solution was added 1N sodium  
hydroxide solution (10ml), and the mixture was refluxed  
for 2 hours, concentrated, neutralized with 1N  
hydrochloric acid and extracted with ethyl acetate. The  
20 organic layer was washed with water and saturated brine  
and dried with anhydrous magnesium sulfate. The solvent  
was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-(4-  
sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-  
carboxylic acid (0.3g) as yellow crystals.  
25 mp 185 - 195°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.1 Hz), 1.27 - 1.46 (2H, m), 1.55 - 1.66 (2H, m), 2.92 (2H, t-like), 3.57 (2H, t, J = 6.6 Hz), 3.82 (2H, t, J = 4.9 Hz), 3.90 (2H, t-like), 4.19 (2H, t, J = 4.9 Hz), 4.73 (2H, s), 6.93 (2H, d, J = 8.8 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.35 (1H, d, J = 8.0 Hz), 7.52 - 7.56 (3H, m), 7.72 - 7.76 (3H, m), 7.85 (1 H s).  
Anal. Calcd. for C<sub>29</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>S: C, 64.91; H, 6.01; N, 5.22.  
Found C, 65.08; H, 6.17; N, 5.03.

## Reference Example 141

10 In dichloromethane (10ml) was dissolved methyl 7-bromo-1-phenyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.4g). Under ice-cooling, to the solution was added dropwise chlorosulfonic acid (0.74ml). The mixture was stirred at room temperature for 30 minutes and, to the  
15 mixture was additionally added chlorosulfonic acid (0.37ml), and the mixture was stirred at room temperature for 30 minutes. The reaction solution was added dropwise to 2M dimethylamine solution in methanol (35ml) under ice-cooling, and the mixture was stirred overnight. The  
20 solvent was evaporated and, to the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give methyl 7-bromo-1-(N,N-  
25 dimethyl-4-sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-

10018321.121201

4-carboxylate (0.37g) as yellow crystals.

mp 210 - 213°C.

$^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{CDCl}_3$ ) 2.69 (6H, s), 2.90 (2H, t,  $J = 5.1$  Hz), 3.79 (3H, s), 3.84 (2H, t,  $J = 5.1$  Hz), 6.89 (2H, d,  $J = 9.2$  Hz), 7.21 (1H, d,  $J = 8.4$  Hz), 7.44 (1H, dd,  $J = 2.2$ , 8.4 Hz), 7.57 - 7.62 (3H, m), 7.68 (1H, d,  $J = 2.2$  Hz).

IR (KBr)  $\nu$ : 2955, 1709, 1595, 1582, 1501, 1483  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{20}\text{H}_{21}\text{BrN}_2\text{O}_4\text{S}$ : C, 51.62; H, 4.55; N, 6.02.

Found C, 51.60; H, 4.55; N, 5.78.

10           Reference Example 142

A mixture of methyl 7-bromo-1-(N,N-dimethyl-4-sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.35g), 4-(2-butoxyethoxy)phenyl borate (0.19g), 1M potassium carbonate solution (2ml), ethanol (2ml) and toluene (50ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.04g), and the mixture was refluxed under argon atmosphere for 6 hours and extracted with ethyl acetate.

20   The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified with silica gel column chromatography (ethyl acetate/hexane) to give methyl 7-

25   [4-(2-butoxyethoxy)phenyl]-1-(N,N-dimethyl-4-

sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.35g) as colorless crystals.

mp 150 - 153°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.3 Hz), 1.35 - 1.66 (4H, m), 2.69 (6H, s), 2.93 (2H, t-like), 3.57 (2H, t, J = 6.6 Hz), 3.80 (3H, s), 3.80 - 3.89 (4H, m), 4.19 (2H, t, J = 5.0 Hz), 6.94 (2H, d, J = 8.8 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.38 (1H, d, J = 8.4 Hz), 7.51 - 7.62 (5H, m), 7.71 (1H, s), 7.78 (1H, s).

IR (KBr) v: 2959, 2868, 1709, 1590, 1495 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>32</sub>H<sub>38</sub>N<sub>2</sub>O<sub>6</sub>S: C, 66.41; H, 6.62; N, 4.84.

Found C, 66.25; H, 6.89; N, 4.76.

#### Reference Example 143

In methanol (50ml) and THF(50ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(N,N-dimethyl-4-sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.34g). To the solution was added 1N sodium hydroxide solution (10ml), and the mixture was stirred at room temperature at 60°C for 1 hour, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-(N,N-dimethyl-4-sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.33g) as

yellow crystals.

mp 236 - 238°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.1 Hz), 1.30 - 1.50 (2H, m), 1.56 - 1.66 (2H, m), 2.69 (6H, s), 2.93 (2H, t-like), 3.57 (2H, t, J = 6.6 Hz), 3.83 (2H, t, J = 4.8 Hz), 3.91 (2H, t-like), 4.19 (2H, t, J = 4.8 Hz), 6.96 (2H, d, J = 9.2 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.39 (1H, d, J = 8.6 Hz), 7.52 - 7.63 (5H, m), 7.72 (1H, d, J = 2.2 Hz), 7.88 (1H, s).

IR (KBr) ν: 2959, 2934, 2872, 1671, 1590, 1501, 1491 cm<sup>-1</sup>.  
Anal. Calcd. for C<sub>31</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>S: C, 65.94; H, 6.43; N, 4.96.  
Found C, 65.82; H, 6.46; N, 4.85.

#### Reference Example 144

In dichloromethane (20ml) was dissolved methyl 7-bromo-1-phenyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1g). Under ice-cooling, to the solution was added dropwise chlorosulfonic acid (0.93ml). The mixture was stirred at room temperature for 1 hour, and the reaction solution was added dropwise to 40% methylamine solution in water (25ml) under ice-cooling. The mixture was stirred at room temperature overnight, concentrated and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give methyl 7-bromo-1-(N-methyl-4-sulfamoylphenyl)-

2,3-dihydro-1H-1-benzazepine-4-carboxylate (1g) as yellow crystals.

mp 201 - 204°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 2.65 (3H, d, J = 5.4 Hz), 2.90 (2H, t, J = 4.6 Hz), 3.79 (3H, s), 3.84 (2H, t, J = 4.6 Hz), 4.23 (1H, q, J = 5.4 Hz), 6.88 (2H, d, J = 9.0 Hz), 7.30 (1H, d, J = 8.8 Hz), 7.44 (1H, dd, J = 2.2, 8.8 Hz), 7.57 - 7.69 (4H, m).

IR (KBr) v: 3277, 2953, 1705, 1595, 1501 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>19</sub>H<sub>19</sub>BrN<sub>2</sub>O<sub>4</sub>S: C, 50.56; H, 4.24; N, 6.21. Found C, 50.62; H, 4.20; N, 6.48.

#### Reference Example 145

A mixture of methyl 7-bromo-1-(N-methyl-4-sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1g), 4-(2-butoxyethoxy)phenyl borate (0.69g), 1M potassium carbonate solution (8ml), ethanol (8ml) and toluene (100ml) was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (0.13g), and the mixture was refluxed under argon atmosphere for 2.5 hours and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was purified with silica gel column chromatography (ethyl

acetate/hexane) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(N-methyl-4-sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.1g) as colorless crystals.

5 mp 142 - 146°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.2 Hz), 1.35 - 1.46 (2H, m), 1.57 - 1.66 (2H, m), 2.65 (3H, d, J = 5.6 Hz), 2.92 (2H, t, J = 4.8 Hz), 3.56 (2H, t, J = 6.6 Hz), 3.80 (3H, s), 3.80 - 3.92 (4H, m), 4.10 - 4.21 (3H, m), 6.92 (2H, 10 d, J = 8.8 Hz), 7.03 (2H, d, J = 8.6 Hz), 7.36 (1H, d, J = 8.4 Hz), 7.50 - 7.56 (3H, m), 7.67 (2H, d, J = 8.8 Hz), 7.71 (1H, d, J = 2.2 Hz), 7.77 (1H, s).

IR (KBr) ν: 2957, 1709, 1590, 1495 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>31</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>S: C, 65.94; H, 6.43; N, 4.69.

15 Found C, 65.76; H, 6.36; N, 4.81.

#### Reference Example 146

In methanol (100ml) and THF (100ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(N-methyl-4-sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4- 20 carboxylate (1.1g). To the solution was added 1N sodium hydroxide solution (19ml), and the mixture was heated at 50°C for 6 hours, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine 25 and dried with anhydrous magnesium sulfate. The solvent

was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-(N-methyl-4-sulfamoylphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1g) as pale yellow crystals.

mp 208 - 210°C.

5 <sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.1 Hz), 1.31 - 1.50 (2H, m), 1.55 - 1.69 (2H, m), 2.65 (3H, d, J = 5.6 Hz), 2.92 (2H, t-like), 3.57 (2H, t, J = 6.6 Hz), 3.82 (2H, t, J = 5.0 Hz), 3.91 (2H, t-like), 4.19 (2H, t, J = 5.0 Hz), 4.27 (1H, q, J = 5.6 Hz), 6.94 (2H, d, J = 8.8 Hz), 7.03 (2H, d, J = 8.6 Hz), 7.37 (1H, d, J = 8.4 Hz), 7.52 - 7.56 (3H, m), 7.67 (2H, d, J = 9.2 Hz), 7.71 (1H, d, J = 2.2 Hz), 7.86 (1H, s).

IR (KBr) ν: 2595, 2932, 2872, 1682, 1493 cm<sup>-1</sup>.

Anal. Calcd. for C<sub>30</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S: C, 65.43; H, 6.22; N, 5.09.

15 Found C, 65.18; H, 6.01; N, 5.02.

#### Working Example 49 (Production of Compound 49)

One droplet of DMF was added to a solution of 1-allyl-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (180mg) in tetrahydrofuran (10ml). Then, thionyl chloride (152mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was  
25 suspended in tetrahydrofuran (30ml), and the suspension



was added to a solution of 4-[[N-methyl N-(tetrahydropyran-4-yl)amino]methyl]aniline (113mg) and triethylamine (516mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate twice. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 1-allyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 49) (125mg) as yellow crystals.

mp 110.0 - 111.0°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.6 Hz), 1.59 - 1.80 (m, 6H), 2.21 (s, 3H), 2.65 (br, 1H), 2.91 (br, 2H), 3.30 - 3.43 (m, 4H) 3.51 (t, 2H, J = 6.8 Hz), 3.57 (s, 2H), 3.80 (t, 2H, J = 4.4 Hz), 3.97 - 4.06 (m, 4H), 4.16 (t, 2H, J = 5.2 Hz), 5.28 (d, 2H, J = 12.8 Hz), 5.95 (br, 1H), 6.89 (d, 1H, J = 8.2 Hz), 6.99 (d, 2H, J = 8.8 Hz), 7.30 (d, 2H, J = 8.4 Hz), 7.37 - 7.56 (m, 8H).

Anal. Calcd. C<sub>38</sub>H<sub>47</sub>N<sub>3</sub>O<sub>4</sub> Calcd. C, 74.18; H, 7.75; N, 6.83.

Found C, 73.87; H, 7.95; N, 6.78.

Working Example 50 (Production of Compound 50)

In toluene (15ml), ethanol (1.5ml) and water (1.5ml) were suspended 1-allyl-7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (262mg), 4-butoxyethoxyphenyl borate (169mg) and potassium carbonate (196mg), and the suspension was stirred under argon atmosphere for 30 minutes. Then, to the mixture was added tetrakis(triphenylphosphine)palladium (45mg), and the mixture was heated under argon atmosphere at 100°C for 6 hours. After allowing to cool, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 16), which was recrystallized from hexane-ethyl acetate to give 1-allyl-7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 50) (46mg) as yellow crystals.

mp 103.0 - 104.0°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.34 -

1.49 (m, 2H), 1.58 - 1.82 (m, 6 Hz), 2.21 (s, 3H), 2.67 (br, 1H), 2.90 (br, 2H), 3.32 - 3.43 (m, 4H), 3.52 - 3.58 (m, 4H), 3.80 (t, 2H, J = 4.8 Hz), 3.93 - 4.10 (m, 4H), 4.16 (t, 2H, J = 4.6 Hz), 5.29 (d, 2H, J = 14.0 Hz), 5.95 (br, 1H),  
5 6.90 (d, 1H, J = 8.6 Hz), 6.98 (d, 2H, J = 8.8 Hz), 7.30 (d, 2H, J = 8.4 Hz), 7.38 - 7.56 (m, 8H).

Working Example 51 (Production of Compound 51)

One droplet of DMF was added to a solution of 1-(2-methoxybenzyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-  
10 benzazepine-4-carboxylic acid (190mg) in tetrahydrofuran (10ml). Then, thionyl chloride (139mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. The solvent and excess thionyl chloride were evaporated  
15 under reduced pressure, the resulting residue was suspended in tetrahydrofuran (25ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (104mg) and triethylamine (476mg) in tetrahydrofuran (10ml) at 0°C.  
20 The suspension was stirred under nitrogen atmosphere at room temperature for 3.5 hours, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated  
25 under reduced pressure, the resulting residue was

separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 1-(2-methoxybenzyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 51) (169mg) as yellow crystals.

mp 118.0 - 119.0°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.4 Hz), 1.59 - 1.82 (m, 6H), 2.21 (s, 3H), 2.65 (br, 1H), 2.89 (br, 2H), 3.30 - 3.42 (m, 4H), 3.51 (t, 2H, J = 7.0 Hz), 3.57 (s, 2H), 3.80 (t, 2H, J = 4.4 Hz), 3.89 (s, 3H), 4.04 (d, 2H, J = 11.0 Hz), 4.16 (t, 2H, J = 5.2 Hz), 4.59 (s, 2H), 6.82 (d, 1H, J = 8.8 Hz), 6.92 - 6.99 (m, 4H), 7.16 (d, 1H, J = 6.6 Hz), 7.28 - 7.35 (m, 4H), 7.43 - 7.56 (m, 7H).

Anal. Calcd. C<sub>43</sub>H<sub>51</sub>N<sub>3</sub>O<sub>5</sub>·0.2H<sub>2</sub>O Calcd. C, 74.47; H, 7.42; N, 6.06. Found C, 74.20; H, 7.53; N, 6.02.

#### Working Example 52 (Production of Compound 52)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(2-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (230mg) in tetrahydrofuran (10ml). Then, thionyl chloride (164mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. The solvent and excess thionyl chloride were evaporated

10018321.121201

under reduced pressure, the resulting residue was suspended in tetrahydrofuran (25ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (121mg) and triethylamine (558mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature for 3.5 hours, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2-methoxybenzyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 52) (236mg) as yellow crystals.

mp 111.5 - 112.5°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.25 - 1.44 (m, 2H), 1.50 - 1.80 (m, 6H), 2.21 (s, 3H), 2.65 (br, 1H), 2.90 (br, 2H), 3.32 - 3.42 (m, 4H), 3.52 - 3.57 (m, 4H), 3.80 (t, 2H, J = 4.4 Hz), 3.89 (s, 3H), 4.04 (d, 2H, J = 11.8 Hz), 4.15 (t, 2H, J = 5.6 Hz), 4.59 (s, 2H), 6.82 (d, 1H, J = 8.8 Hz), 6.92 - 6.99 (m, 4H), 7.16 (d, 1H, J = 6.6

Hz), 7.26 - 7.32 (m, 4H), 7.44 - 7.57 (m, 7H).

Anal. Calcd.  $C_{44}H_{53}N_3O_5 \cdot 0.1H_2O$  Calcd. C, 74.88; H, 7.60; N, 5.96: Found C, 74.62; H, 7.39; N, 5.89.

Working Example 53 (Production of Compound 53)

5 One droplet of DMF was added to a solution of 1-(3-methoxybenzyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (110mg) in tetrahydrofuran (10ml). Then, thionyl chloride (80mg) was added at 0°C, the temperature was returned to room temperature, and the  
10 mixture was stirred under nitrogen atmosphere for 1 hour. The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was suspended in tetrahydrofuran (25ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (60mg) and  
15 triethylamine (273mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature for 5 hours, to the mixture was added water, and the mixture was extracted with ethyl acetate.  
20 The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which  
25 was recrystallized from hexane-ethyl acetate to give 1-

(3-methoxybenzyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 53) (62mg) as yellow crystals.

5 mp 113.0 - 114.0°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.2 Hz), 1.56 - 1.80 (m, 6H), 2.21 (s, 3H), 2.62 (br, 1H), 2.86 (br, 2H), 3.32 - 3.45 (m, 4H), 3.51 (t, 2H, J = 6.6 Hz), 3.57 (s, 2H), 3.78 - 3.83 (m, 5H), 4.03 (d, 2H, J = 9.8 Hz), 4.16 (t, 2H, J = 5.2 Hz), 4.58 (s, 2H), 6.82 - 6.92 (m, 4H), 6.98 (d, 2H, J = 8.8 Hz), 7.26 - 7.38 (m, 4H), 7.45 - 7.56 (m, 7H).

Working Example 54 (Production of Compound 54)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(3-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (150mg) in tetrahydrofuran (10ml). Then, thionyl chloride (107mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was suspended in tetrahydrofuran (25ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (79mg) and triethylamine (363mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at

room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated

5 under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(3-methoxybenzyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 54) (29mg) as yellow crystals.

mp 107.5 - 108.5°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.33 - 1.45 (m, 2H), 1.57 - 1.80 (m, 6H), 2.21 (s, 3H), 2.64 (br, 1H), 2.86 (br, 2H), 3.32 - 3.45 (m, 4H), 3.55 (t, 2H, J = 6.6 Hz), 3.57 (s, 2H), 3.78 - 3.83 (m, 5H), 4.03 (d, 2H, J = 9.4 Hz), 4.16 (t, 2H, J = 5.0 Hz), 4.58 (s, 2H), 6.82 - 6.92 (m, 4H), 6.97 (d, 2H, J = 8.8 Hz), 7.26 - 7.39 (m, 4H), 7.44 - 7.55 (m, 7H).

Anal. Calcd. C<sub>44</sub>H<sub>53</sub>N<sub>3</sub>O<sub>5</sub> Calcd. C, 75.08; H, 7.59; N, 5.97. Found C, 74.74; H, 7.52; N, 5.91.

#### Working Example 55 (Production of Compound 55)

One droplet of DMF was added to a solution of 1-(4-methoxybenzyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-



benzazepine-4-carboxylic acid (110mg) in tetrahydrofuran (10ml). Then, thionyl chloride (96mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour.

- 5 The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was suspended in tetrahydrofuran (30ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (71mg) and
- 10 triethylamine (328mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and
- 15 dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 1-
- 20 (4-methoxybenzyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 55) (86mg) as yellow crystals.

mp 160.0 - 161.0°C

- 25 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.8 Hz), 1.58 -

1.80 (m, 6H), 2.21 (s, 3H), 2.64 (br, 1H), 2.81 (br, 2H),  
 3.32 - 3.42 (m, 4H), 3.51 (t, 2H, J = 6.6 Hz), 3.57 (s, 2H),  
 3.78 - 3.82 (m, 5H), 4.03 (d, 2H, J = 9.4 Hz), 4.16 (t, 2H,  
 J = 5.2 Hz), 4.54 (s, 2H), 6.89 - 7.00 (m, 5H), 7.22 - 7.41  
 5 (m, 5H), 7.45 - 7.56 (m, 7H).

Anal. Calcd.  $C_{43}H_{51}N_3O_5 \cdot 0.4H_2O$  Calcd. C, 74.08; H, 7.43; N, 6.03. Found C, 73.82; H, 7.60; N, 5.99.

#### Working Example 56 (Production of Compound 56)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(4-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (140mg) in tetrahydrofuran (10ml). Then, thionyl chloride (100mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour.

15 The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was suspended in tetrahydrofuran (25ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (74mg) and

20 triethylamine (344mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature for 3.5 hours, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and

25 dried with magnesium sulfate. The solvent was evaporated

under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 7-

5 (4-butoxyethoxyphenyl)-1-(4-methoxybenzyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 56) (89mg) as yellow crystals.

mp 151.0 - 152.0°C

10 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz),, 1.26 - 1.46 (m, 2H), 1.50 - 1.80 (m, 6H), 2.21 (s, 3H), 2.64 (br, 1H), 2.81 (br, 2H), 3.28 - 3.42 (m, 4H), 3.52 - 3.60 (m, 4H), 3.77 - 3.82 (m, 5H), 4.03 (d, 2H, J = 10.2 Hz), 4.16 (t, 2H, J = 5.0 Hz), 4.54 (s, 2H), 6.89 - 7.22 (m, 5H),

15 7.20 - 7.40 (m, 5H), 7.45 - 7.56 (m, 7H).

Anal. Calcd. C<sub>44</sub>H<sub>53</sub>N<sub>3</sub>O<sub>5</sub> · 0.3H<sub>2</sub>O Calcd. C, 74.50; H, 7.62; N, 5.93. Found C, 74.34; H, 7.62; N, 5.96.

#### Working Example 57 (Production of Compound 57)

One droplet of DMF was added to a solution of 7-(4-propoxyethoxyphenyl)-1-(3-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (250mg) in tetrahydrofuran (10ml). Then, thionyl chloride (193mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour.

25 The solvent and excess thionyl chloride were evaporated

under reduced pressure, the resulting residue was suspended in tetrahydrofuran (25ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (143mg) and triethylamine (655mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-1-(3-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 57) (260mg) as yellow crystals.

mp 131.5 - 132.5°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.4 Hz), 1.58 - 1.80 (m, 6H), 2.21 (s, 3H), 2.64 (br, 1H), 2.84 (br, 2H), 3.32 - 3.42 (m, 4H), 3.51 (t, 2H, J = 7.0 Hz), 3.57 (s, 2H), 3.81 (t, 2H, J = 4.2 Hz), 4.03 (d, 2H, J = 10.6 Hz), 4.16 (t, 2H, J = 5.2 Hz), 4.58 (s, 2H), 6.93 - 7.06 (m, 4H), 7.16 (br, 1H), 7.28 - 7.42 (m, 4H), 7.45 - 7.55 (m, 7H).

Anal. Calcd.  $C_{40}H_{47}N_3O_4S \cdot 0.1H_2O$  Calcd. C, 71.95; H, 7.13; N, 6.29. Found C, 71.66; H, 7.12; N, 6.22.

Working Example 58 (Production of Compound 58)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(3-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (250mg) in tetrahydrofuran (10ml). Then, thionyl chloride (187mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour.

The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was suspended in tetrahydrofuran (25ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (131mg) and triethylamine (638mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-

(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(3-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 58) (233mg) as yellow crystals.

mp 122.0 - 123.0°C

- 5  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (t, 3H,  $J = 7.2$  Hz), 1.34 - 1.50 (m, 2H), 1.60 - 1.75 (m, 6H), 2.21 (s, 3H), 2.60 (br, 1H), 2.84 (br, 2H), 3.32 - 3.45 (m, 4H), 3.52 - 3.58 (m, 4H), 3.80 (t, 2H,  $J = 4.0$  Hz), 4.05 (d, 2H,  $J = 12.2$  Hz), 4.16 (t, 2H,  $J = 5.0$  Hz), 4.58 (s, 2H), 6.93 - 7.06 (m, 4H),  
10 7.16 (br, 1H), 7.32 - 7.42 (m, 4H), 7.45 - 7.55 (m, 7H).  
Anal. Calcd.  $\text{C}_{41}\text{H}_{49}\text{N}_3\text{O}_4\text{S}$  Calcd. C, 72.43; H, 7.26; N, 6.18.  
Found C, 72.03; H, 7.44; N, 6.12.

#### Working Example 59 (Production of Compound 59)

- One droplet of DMF was added to a solution of 7-(4-propoxyethoxyphenyl)-1-(2-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (240mg) in tetrahydrofuran (10ml). Then, thionyl chloride (184mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour.  
20 The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was suspended in tetrahydrofuran (30ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (137mg) and  
25 triethylamine (629mg) in tetrahydrofuran (10ml) at 0°C.

The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-1-(2-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 59) (152mg) as yellow crystals.

mp 104.5 - 105.5°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.2 Hz), 1.57 - 1.80 (m, 6H), 2.21 (s, 3H), 2.62 (br, 1H), 2.88 (br, 2H), 3.32 - 3.41 (m, 4H), 3.51 (t, 2H, J = 6.6 Hz), 3.57 (s, 2H), 3.81 (t, 2H, J = 4.8 Hz), 4.04 (d, 2H, J = 11.4 Hz), 4.16 (t, 2H, J = 5.2 Hz), 4.73 (s, 2H), 6.96 - 7.05 (m, 5H), 7.26 - 7.32 (m, 3H), 7.40 - 7.60 (m, 8H).

Anal. Calcd. C<sub>40</sub>H<sub>47</sub>N<sub>3</sub>O<sub>4</sub>S Calcd. C, 72.15; H, 7.11; N, 6.31. Found C, 71.87; H, 6.92; N, 6.26.

Working Example 60 (Production of Compound 60)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(2-thienylmethyl)-2,3-dihydro-1-

benzazepine-4-carboxylic acid (110mg) in tetrahydrofuran (10ml). Then, thionyl chloride (82mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour.

- 5 The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was suspended in tetrahydrofuran (20ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (61mg) and
- 10 triethylamine (279mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature for 3 hours, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and
- 15 dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 7-
- 20 (4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(2-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 60) (86mg) as yellow crystals.

mp 84.0 - 85.0°C

- 25 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 2H, J = 7.2 Hz), 1.34 -



1.50 (m, 2H), 1.59- 1.80 (m, 6H), 2.22 (s, 3H), 2.66 (br, 1H), 2.89 (br, 2H), 3.30 - 3.45 (m, 4H), 3.55 (t, 2H, J = 6.6 Hz), 3.58 (s, 2H), 3.80 (t, 2H, J = 4.0 Hz), 4.04 (d, 2H, J = 12.6 Hz), 4.16 (t, 2H, J = 5.4 Hz), 4.73 (s, 2H),  
5 6.96 - 7.06 (m, 5H), 7.29 - 7.33 (m, 3H), 7.45 - 7.56 (m, 8H).

Anal. Calcd.  $C_{41}H_{49}N_3O_4S$  Calcd. C, 71.29; H, 7.33; N, 6.08.  
Found C, 71.14; H, 7.12; N, 6.01.

Working Example 61 (Production of Compound 61)

10 One droplet of DMF was added to a solution of 1-(3-furylmethyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (200mg) in tetrahydrofuran (10ml). Then, thionyl chloride (159mg) was added at 0°C, the temperature was returned to room temperature, and the  
15 mixture was stirred under nitrogen atmosphere for 1 hour. The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was suspended in tetrahydrofuran (25ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (118mg) and  
20 triethylamine (546mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature for 4.5 hours, to the mixture was added water, and the mixture was extracted with ethyl acetate.  
25 The organic layer was washed with saturated brine and

10018324.121204

dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 1-(3-furylmethyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 61) (153mg) as yellow crystals.

mp 115.0 - 116.0°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.2 Hz), 1.59 - 1.85 (m, 6H), 2.21 (s, 3H), 2.65 (br, 1H), 2.85 (br, 2H), 3.32 - 3.43 (m, 4H), 3.51 (t, 2H, J = 6.6 Hz), 3.57 (s, 2H), 3.81 (t, 2H, J = 4.4 Hz), 4.04 (d, 2H, J = 14.6 Hz), 4.17 (t, 2H, J = 5.6 Hz), 4.41 (s, 2H), 6.40 (s, 1H), 6.96 - 7.01 (m, 3H), 7.30 (d, 2H, J = 8.8 Hz), 7.43 - 7.56 (m, 10H).

Anal. Calcd. C<sub>40</sub>H<sub>47</sub>N<sub>3</sub>O<sub>5</sub> Calcd. C, 73.93; H, 7.29; N, 6.47. Found C, 73.53; H, 7.32; N, 6.38.

Working Example 62 (Production of Compound 62)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(3-furylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (200mg) in tetrahydrofuran (10ml). Then, thionyl chloride (155mg) was added at 0°C, the temperature was returned to room temperature, and the

10018324-121301

mixture was stirred under nitrogen atmosphere for 1 hour. The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was suspended in tetrahydrofuran (25ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (115mg) and triethylamine (526mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature for 4.5 hours, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(3-furylmethyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 62) (125mg) as yellow crystals.

mp 116.0 - 117.0°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.25 - 1.45 (m, 2H), 1.58 - 1.81 (m, 6H), 2.21 (s, 3H), 2.65 (br, 1H), 2.84 (br, 2H), 3.32 - 3.43 (m, 4H), 3.56 (t, 2H, J = 7.0 Hz), 3.57 (s, 2H), 3.80 (t, 2H, J = 4.8 Hz), 4.04 (d,

2H, J = 10.6 Hz), 4.16 (t, 2H, J = 5.4 Hz), 4.41 (s, 2H),  
6.40 (d, 1H, J = 0.8 Hz), 6.96 - 7.01 (m, 3H), 7.30 (d, 2H,  
J = 8.8 Hz), 7.38 - 7.56 (m, 10H).

Anal. Calcd.  $C_{41}H_{49}N_3O_5 \cdot 0.2H_2O$  Calcd. C, 73.81; H, 7.41; N,  
5 6.30. Found C, 73.71; H, 7.43; N, 6.18.

Working Example 63 (Production of Compound 63)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(2-ethoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (200mg) in tetrahydrofuran  
10 (10ml). Then, thionyl chloride (138mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. The solvent and excess thionyl chloride were evaporated under reduced pressure, the resulting residue was  
15 suspended in tetrahydrofuran (30ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (103mg) and triethylamine (476mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at  
20 room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was  
25 separated and purified with silica gel column

chromatography (methanol : ethyl acetate = 1 : 8), which  
was recrystallized from hexane-ethyl acetate to give 7-  
(4-butoxyethoxyphenyl)-1-(2-ethoxybenzyl)-N-[4-[[N-  
methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-  
5 dihydro-1-benzazepine-4-carboxamide (Compound 63) (161mg)  
as yellow crystals.

mp 104.5 - 105.5°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.32 -  
1.47 (m, 5H), 1.56 - 1.80 (m, 6H), 2.21 (s, 3H), 2.63 (br,  
10 1H), 2.90 (br, 2H), 3.32 - 3.42 (m, 4H), 3.52 - 3.57 (m,  
4H), 3.80 (t, 2H, J = 4.8 Hz), 4.01 - 4.18 (m, 6H), 4.60 (s,  
2H), 6.84 (d, 1H, J = 8.8 Hz), 6.89 - 6.99 (m, 5H), 7.16 (d,  
1H, J = 6.2 Hz), 7.27 - 7.37 (m, 4H), 7.44 - 7.56 (m, 6H).

Anal. Calcd. C<sub>45</sub>H<sub>55</sub>N<sub>3</sub>O<sub>5</sub> Calcd. C, 75.28; H, 7.72; N, 5.85.  
15 Found C, 74.94; H, 7.77; N, 5.67.

#### Working Example 64 (Production of Compound 64)

One droplet of DMF was added to a solution of 7-(4-  
butoxyethoxyphenyl)-1-(3-propoxybenzyl)-2,3-dihydro-1-  
benzazepine-4-carboxylic acid (200mg) in tetrahydrofuran  
20 (10ml). Then, thionyl chloride (134mg) was added at 0°C,  
the temperature was returned to room temperature, and the  
mixture was stirred under nitrogen atmosphere for 1 hour.  
The solvent and excess thionyl chloride were evaporated  
under reduced pressure, the resulting residue was  
25 suspended in tetrahydrofuran (30ml), and the suspension

was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (100mg) and triethylamine (455mg) in tetrahydrofuran (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature for 4.5 hours, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(3-propoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 64) (207mg) as yellow crystals.

mp 114.5 - 115.5°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.02 (t, 3H, J = 7.4 Hz), 1.34 - 1.45 (m, 2H), 1.57 - 1.85 (m, 8H), 2.21 (s, 3H), 2.63 (br, 1H), 2.86 (br, 2H), 3.30 - 3.46 (m, 4H), 3.52 - 3.59 (m, 4H), 3.80 (t, 2H, J = 4.0 Hz), 3.91 (t, 2H, J = 6.6 Hz), 4.04 (d, 2H, J = 10.4 Hz), 4.16 (t, 2H, J = 5.2 Hz), 4.57 (s, 2H), 6.85 - 7.00 (m, 6H), 7.26 - 7.40 (m, 4H), 7.45 - 7.56 (m, 7H).

Anal. Calcd. C<sub>46</sub>H<sub>57</sub>N<sub>3</sub>O<sub>5</sub> Calcd. C, 75.48; H, 7.85; N, 5.74.

Found C, 75.21; H, 7.85; N, 5.64.

Working Example 65 (Production of Compound 65)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(2,5-dimethoxybenzyl)-2,3-dihydro-  
5 1-benzazepine-4-carboxylic acid (200mg) in tetrahydrofuran (10ml). Then, thionyl chloride (134mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. The solvent and excess thionyl  
10 chloride were evaporated under reduced pressure, the resulting residue was suspended in tetrahydrofuran (30ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (100mg) and triethylamine (455mg) in tetrahydrofuran  
15 (10ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was  
20 evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2,5-dimethoxybenzyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-  
25

dihydro-1-benzazepine-4-carboxamide (Compound 65) (210mg)  
as yellow crystals.

mp 143.0 - 144.0°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.32 -  
5 1.45 (m, 2H), 1.56 - 1.80 (m, 6H), 2.21 (s, 3H), 2.65 (br,  
1H), 2.90 (br, 2H), 3.32 - 3.47 (m, 4H), 3.55 (t, 2H, J =  
2.0 Hz), 3.57 (s, 2H), 3.71 (s, 3H), 3.80 (t, 2H, J = 4.0  
Hz), 3.84 (s, 3H), 4.04 (d, 2H, J = 14.2 Hz), 4.16 (t, 2H,  
J = 5.6 Hz), 4.56 (s, 2H), 6.76 - 6.89 (m, 4H), 6.97 (d, 2H,  
10 J = 8.8 Hz), 7.26 - 7.36 (m, 3H), 7.44 - 7.56 (m, 7H).

Anal. Calcd. C<sub>45</sub>H<sub>55</sub>N<sub>3</sub>O<sub>6</sub> Calcd. C, 73.64; H, 7.55; N, 5.73.  
Found C, 73.37; H, 7.63; N, 5.66.

#### Working Example 66 (Production of Compound 66)

One droplet of DMF was added to a solution of 7-(4-  
15 butoxyethoxyphenyl)-1-(2-fluorobenzyl)-2,3-dihydro-1-  
benzazepine-4-carboxylic acid (200mg) in tetrahydrofuran  
(10ml). Then, thionyl chloride (146mg) was added at 0°C,  
the temperature was returned to room temperature, and the  
mixture was stirred under nitrogen atmosphere for 1 hour.  
20 The solvent and excess thionyl chloride were evaporated  
under reduced pressure, the resulting residue was  
suspended in tetrahydrofuran (30ml), and the suspension  
was added to a solution of 4-[[N-methyl-N-  
(tetrahydropyran-4-yl)amino]methyl]aniline (108mg) and  
25 triethylamine (496mg) in tetrahydrofuran (10ml) at 0°C.



The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8) to give 7-(4-butoxyethoxyphenyl)-1-(2-fluorobenzyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 66) (139mg) as yellow amorphous.

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (t, 3H,  $J = 7.2$  Hz), 1.30 - 1.50 (m, 2H), 1.51 - 1.82 (m, 6H), 2.21 (s, 3H), 2.64 (br, 1H), 2.88 (br, 2H), 3.30 - 3.45 (m, 4H), 3.50 - 3.62 (m, 4H), 3.80 (t, 2H,  $J = 4.4$  Hz), 4.04 (d, 2H,  $J = 11.0$  Hz), 4.16 (t, 2H,  $J = 5.0$  Hz), 4.65 (s, 2H), 6.86 (d, 1H,  $J = 8.6$  Hz), 6.98 (d, 2H,  $J = 8.8$  Hz), 7.07 - 7.16 (m, 2H), 7.20 - 7.60 (m, 12H).

Anal. Calcd.  $\text{C}_{43}\text{H}_{50}\text{N}_3\text{O}_4 \cdot 0.8\text{H}_2\text{O}$  Calcd. C, 73.13; H, 7.14; N, 5.95: Found, C, 72.93; H, 7.22; N, 5.79.

#### Working Example 67 (Production of Compound 67)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-[(1-methylimidazol-2-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (140mg) in

tetrahydrofuran (10ml). Then, thionyl chloride (41mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. Then, this mixture was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (75mg) and triethylamine (346mg) in tetrahydrofuran (30ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with basic silica gel column chromatography (ethyl acetate), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(1-methylimidazol-2-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 67) (65mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.30 - 1.45 (m, 2H), 1.55 - 1.80 (m, 6H), 2.20 (s, 3H), 2.51 (br, 2H), 2.64 (br, 1H), 3.30 - 3.45 (m, 4H), 3.52 - 3.59 (m, 5H), 3.81 (t, 2H, J = 4.8 Hz), 4.04 (d, 2H, J = 10.2 Hz), 4.17 (t, 2H, J = 5.2 Hz), 4.62 (s, 2H), 4.79 (s, 2H), 6.90

(d, 1H, J = 1.2 Hz), 6.97 - 7.01 (m, 3H), 7.07 (d, 1H, J = 8.0 Hz), 7.27 - 7.32 (m, 2H), 7.46 - 7.57 (m, 8H).

Working Example 68 (Production of Compound 68)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(thiazol-2-yl)methyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (70mg) in dichloromethane (10ml). Then, thionyl chloride (23mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour.

Then, this solution was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (42mg) and triethylamine (385mg) in dichloromethane (20ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 3) to give 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(thiazol-2-yl)methyl-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 68) (66mg) as yellow amorphous.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.33 -

1.45 (m, 2H), 1.58 - 1.80 (m, 6H), 2.21 (s, 3H), 2.65 (br, 1H), 2.95 (br, 2H), 3.30 - 3.57 (m, 8H), 3.80 (t, 2H, J = 4.0 Hz), 4.04 (d, 2H, J = 10.4 Hz), 4.16 (t, 2H, J = 5.0 Hz), 4.88 (s, 2H), 6.96 - 7.03 (m, 3H), 7.26 - 7.60 (m, 8H),  
5 7.80 (d, 1H, J = 3.2 Hz).

Anal. Calcd.  $C_{40}H_{48}N_4O_4S$  Calcd. C, 70.56; H, 7.11; N, 8.23.  
Found C, 70.38; H, 7.12; N, 8.18.

Working Example 69 (Production of Compound 69)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (380mg) in  
10 dichloromethane (20ml). Then, thionyl chloride (124mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen  
15 atmosphere for 1 hour. Then, this solution was added to a solution of 4-[[N-methyl N-(tetrahydropyran-4-yl)amino]methyl]aniline (229mg) and triethylamine (2.1g) in dichloromethane (30ml) at 0°C. The suspension was  
20 stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with  
25 magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column chromatography

(methanol : ethyl acetate = 1 : 3), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrazol-4-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-

5 yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 69) (338mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 - 1.45 (m, 2H), 1.50 - 1.80 (m, 6H), 2.21 (s, 3H), 2.63 (br, 1H), 2.85 (br, 2H), 3.28 - 3.45 (m, 4H), 3.52 - 3.59 (m, 10 4H), 3.80 (t, 2H, J = 4.0 Hz), 3.90 (s, 3H), 4.04 (d, 2H, J = 11.6 Hz), 4.16 (t, 2H, J = 5.4 Hz), 4.44 (s, 2H), 6.96 - 7.01 (m, 3H), 7.15 - 7.22 (m, 3H), 7.26 - 7.39 (m, 3H), 7.45 - 7.55 (m, 9H).

Anal. Calcd. C<sub>41</sub>H<sub>51</sub>N<sub>5</sub>O<sub>4</sub> Calcd. C, 72.64; H, 7.58; N, 10.33.  
15 Found C, 72.34; H, 7.59; N, 10.34.

#### Working Example 70 (Production of Compound 70)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (200mg) in  
20 tetrahydrofuran (10ml). Then, thionyl chloride (150mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. Then, this mixture was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-  
25 yl)amino]methyl]aniline (111mg) and triethylamine (1.0g)

in tetrahydrofuran (25ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with basic silica gel column chromatography (methanol : ethyl acetate = 1 : 3) to give 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrazol-5-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 70) (60mg) as yellow amorphous.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.34 - 1.45 (m, 2H), 1.50 - 1.80 (m, 6H), 2.21 (s, 3H), 2.40 - 2.70 (m, 3H), 3.30 - 3.45 (m, 4H), 3.52 - 3.59 (m, 4H), 3.79 - 3.84 (m, 5H), 4.04 (d, 2H, J = 10.6 Hz), 4.17 (t, 2H, J = 5.2 Hz), 4.55 (s, 2H), 6.25 (d, 1H, J = 1.8 Hz), 6.93 - 7.02 (m, 3H), 7.30 (d, 2H, J = 8.4 Hz), 7.42 - 7.57 (m, 9H).

Anal. Calcd. C<sub>41</sub>H<sub>51</sub>N<sub>5</sub>O<sub>4</sub> · 0.2H<sub>2</sub>O Calcd. C, 72.26; H, 7.60; N, 10.28. Found C, 72.02; H, 7.46; N, 10.03.

#### Working Example 71 (Production of Compound 71)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-[(3,5-dimethylisoxazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid

(140mg) in tetrahydrofuran (10ml). Then, thionyl chloride (102mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. Then, this mixture  
5 was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (75mg) and triethylamine (690mg) in tetrahydrofuran (25ml) at 0°C. The suspension was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added  
10 water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was separated and purified with silica gel column  
15 chromatography (methanol : ethyl acetate = 1 : 3) to give 7-(4-butoxyethoxyphenyl)-1-[(3,5-dimethylisoxazol-4-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 71) (45mg) as yellow amorphous.  
20 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.33 - 1.45 (m, 2H), 1.50 - 1.80 (m, 6H), 2.22 (s, 6H), 2.41 (s, 3H), 2.67 (br, 2H), 3.20 (br, 2H), 3.30 - 3.44 (m, 2H), 3.52 - 3.59 (m, 4H), 3.81 (t, 2H, J = 4.8 Hz), 4.04 (d, 2H, J = 9.2 Hz), 4.17 (t, 2H, J = 5.4 Hz), 4.29 (s, 2H), 6.95 -  
25 7.02 (m, 3H), 7.31 (d, 2H, J = 8.4 Hz), 7.42 - 7.57 (m, 8H).

Anal. Calcd.  $C_{42}H_{52}N_4O_5 \cdot 0.2H_2O$  Calcd. C, 72.42; H, 7.52; N, 8.04. Found C, 72.15; H, 7.72; N, 7.81.

Working Example 72 (Production of Compound 72)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(2-furylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (200mg) in tetrahydrofuran (10ml). Then, thionyl chloride (155mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. Then, the solvent and excess thionyl chloride were evaporated, and the resulting residue was suspended in tetrahydrofuran (15ml) and added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (115mg) and triethylamine (1.1g) in tetrahydrofuran (10ml) at 0°C. The mixture was stirred under nitrogen atmosphere at room temperature for 2.5 hours, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2-furylmethyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-



dihydro-1-benzazepine-4-carboxamide (Compound 72) (199mg)  
as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.37 -  
1.48 (m, 2H), 1.58 - 1.80 (m, 6H), 2.22 (s, 3H), 2.65 (br,  
5 1H), 2.85 (br, 2H), 3.27 - 3.46 (m, 4H), 3.52 - 3.57 (m,  
4H), 3.81 (t, 2H, J = 4.6 Hz), 4.03 (d, 2H, J = 11.8 Hz),  
4.16 (t, 2H, J = 4.8 Hz), 4.51 (s, 2H), 6.29 (d, 1H, J =  
3.2 Hz), 6.38 (dd, 1H, J = 2.8, 1.8 Hz), 6.98 (d, 2H, J =  
8.8 Hz), 7.09 (d, 1H, J = 8.8 Hz), 7.31 (d, 2H, J = 8.6 Hz),  
10 7.40 - 7.56 (m, 9H).

Anal. Calcd. C<sub>41</sub>H<sub>49</sub>N<sub>3</sub>O<sub>5</sub>·0.1H<sub>2</sub>O Calcd. C, 73.97; H, 7.42; N,  
6.31. Found C, 73.77; H, 7.24; N, 6.28.

#### Working Example 73 (Production of Compound 73)

One droplet of DMF was added to a solution of 7-(4-  
15 butoxyethoxyphenyl)-1-(2-pyridylmethyl)-2,3-dihydro-1-  
benzazepine-4-carboxylic acid (50mg) in dichloromethane  
(5ml). Then, thionyl chloride (17mg) was added at 0°C,  
the temperature was returned to room temperature, and the  
mixture was stirred under nitrogen atmosphere for 1 hour.  
20 Then, this solution was added to a solution of 4-[[N-  
methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline  
(31mg) and triethylamine (287mg) in dichloromethane  
(15ml) at 0°C. The mixture was stirred under nitrogen  
atmosphere at room temperature overnight, to the mixture  
25 was added water, and the mixture was extracted with ethyl

acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 3) to give 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-1-(2-pyridylmethyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 73) (31mg) as yellow amorphous.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.30 - 1.44 (m, 2H), 1.52 - 1.82 (m, 6H), 2.22 (s, 3H), 2.65 (br, 1H), 2.93 (br, 2H), 3.30 - 3.58 (m, 8H), 3.80 (t, 2H, J = 4.4 Hz), 4.04 (d, 2H, J = 10.6 Hz), 4.15 (t, 2H, J = 5.2 Hz), 4.73 (s, 2H), 6.85 (d, 1H, J = 8.6 Hz), 6.97 (d, 2H, J = 8.6 Hz), 7.20 - 7.37 (m, 5H), 7.44 - 7.71 (m, 8H), 8.65 (d, 1H, J = 5.2 Hz).

#### Working Example 74 (Production of Compound 74)

To a solution of 7-(4-butoxyethoxyphenyl)-N-[4-[[methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (150mg) and 1-methylpyrrol-2-carboxyaldehyde (140mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxymethylborohydride (326mg). The mixture was stirred under nitrogen atmosphere at room temperature for 4 days and, then, water was added thereto, and the mixture was

extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 6) to give 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrrol-2-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 74) (8mg) as yellow amorphous.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.30 - 1.49 (m, 2H), 1.54 - 1.85 (m, 6H), 2.21 (s, 3H), 2.50 (br, 2H), 2.65 (br, 1H), 3.25 - 3.59 (m, 11H), 3.81 (t, 2H, J = 4.4 Hz), 4.04 (d, 2H, J = 11.8 Hz), 4.17 (t, 2H, J = 5.2 Hz), 4.47 (s, 2H), 6.11 (t, 1H, J = 2.8 Hz), 6.16 (s, 1H), 6.66 (s, 1H), 6.97 - 7.06 (m, 3H), 7.29 (d, 2H, J = 9.8 Hz), 7.46 - 7.56 (m, 8H).

#### Working Example 75 (Production of Compound 75)

To a solution of 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (130mg) and 2-methyloxazol-4-carboxyaldehyde (100mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxaborohydride (378mg). The mixture was stirred under nitrogen atmosphere at room temperature for 5 days

and, then, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with basic silica gel column chromatography (hexane : ethyl acetate = 1 : 2) to give 7-(4-butoxyethoxyphenyl)-1-[(2-methyloxazol-4-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 75) (29mg) as yellow amorphous.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.34 - 1.45 (m, 2H), 1.54 - 1.80 (m, 6H), 2.21 (s, 3H), 2.48 (s, 3H), 2.63 (br, 1H), 2.90 (br, 2H), 3.30 - 3.45 (m, 4H), 3.52 - 3.58 (m, 4H), 3.80 (t, 2H, J = 4.6 Hz), 4.04 (d, 2H, J = 11.4 Hz), 4.16 (t, 2H, J = 4.4 Hz), 4.43 (s, 2H), 6.96 - 7.05 (m, 3H), 7.30 (d, 2H, J = 8.4 Hz), 7.38 - 7.55 (m, 9H).

Working Example 76 (Production of Compound 76)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-[(2-methylthiazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (150mg) in chloroform (10ml). Then, thionyl chloride (47mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen

atmosphere for 1 hour. Then, this solution was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (87mg) and triethylamine (800mg) in chloroform (20ml) at 0°C. The mixture was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 3) to give 7-(4-butoxyethoxyphenyl)-1-[(2-methylthiazol-4-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 76) (37mg) as yellow amorphous.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.34 - 1.45 (m, 2H), 1.50 - 1.82 (m, 6H), 2.22 (s, 3H), 2.66 (br, 1H), 2.74 (s, 3H), 2.91 (br, 2H), 3.30 - 3.48 (m, 4H), 3.52 - 3.58 (m, 4H), 3.80 (t, 2H, J = 4.4 Hz), 4.04 (d, 2H, J = 11.4 Hz), 4.16 (t, 2H, J = 5.4 Hz), 4.67 (s, 2H), 6.92 - 7.00 (m, 4H), 7.26 - 7.60 (m, 10H).

#### Working Example 77 (Production of Compound 77)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-[(3-methylthiazol-5-yl)methyl]-2,3-

dihydro-1-benzazepine-4-carboxylic acid (150mg) in  
 dichloromethane (10ml). Then, thionyl chloride (47mg)  
 was added at 0°C, the temperature was returned to room  
 temperature, and the mixture was stirred under nitrogen  
 5 atmosphere for 1 hour. Then, this solution was added to  
 a solution of 4-[[N-methyl-N-(tetrahydropyran-4-  
 yl)amino]methyl]aniline (87mg) and triethylamine (800mg)  
 in dichloromethane (20ml) at 0°C. The mixture was  
 stirred under nitrogen atmosphere at room temperature  
 10 overnight, to the mixture was added water, and the  
 mixture was extracted with ethyl acetate. The organic  
 layer was washed with saturated brine and dried with  
 magnesium sulfate. The solvent was evaporated under  
 reduced pressure, and the resulting residue was separated  
 15 and purified with silica gel column chromatography  
 (methanol : ethyl acetate = 1 : 3), which was  
 recrystallized from hexane-ethyl acetate to give 7-(4-  
 butoxyethoxyphenyl)-1-[(3-methylisothiazol-5-yl)methyl]-  
 N-[4-[[N-methyl-N-(tetrahydropyran-5-  
 20 yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-  
 carboxamide (Compound 77) (96mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 6.8 Hz), 1.34 -  
 1.45 (m, 2H), 1.50 - 1.80 (m, 6H), 2.21 (s, 3H), 2.49 (s,  
 3H), 2.64 (br, 1H), 2.94 (br, 2H), 3.31 - 3.41 (m, 4H),  
 25 3.52 - 3.58 (m, 4H), 3.80 (t, 2H, J = 4.4 Hz), 4.04 (d, 2H,

$J = 10.2$  Hz), 4.16 (t, 2H,  $J = 5.4$  Hz), 4.79 (s, 2H), 6.90 - 7.01 (m, 4H), 7.31 (d, 2H,  $J = 8.8$  Hz), 7.38 - 7.56 (m, 8H).

Anal. Calcd.  $C_{41}H_{50}N_4O_4S$  Calcd. C, 70.86; H, 7.25; N, 8.06.

5 Found C, 70.57; H, 7.01; N, 8.02.

Working Example 78 (Production of Compound 78)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-(2-thienylcarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (100mg) in dichloromethane  
10 (10ml). Then, thionyl chloride (31mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. Then, this solution was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline  
15 (57mg) and triethylamine (520mg) in dichloromethane (20ml) at 0°C. The mixture was stirred under nitrogen atmosphere at room temperature overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated  
20 brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 3), which was recrystallized hexane-ethyl acetate to give 7-  
25 (4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-

(tetrahydropyran-5-yl)amino]methyl]phenyl]-1-(2-thienylcarbonyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 78) (43mg) as colorless crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.4 Hz), 1.34 - 1.45 (m, 2H), 1.50 - 1.81 (m, 6H), 2.21 (s, 3H), 2.62 (br, 1H), 3.10 (br, 2H), 3.37 (td, 2H, J = 10.6, 2.8 Hz), 3.53 - 3.59 (m, 4H), 3.82 (t, 2H, J = 4.4 Hz), 4.04 (d, 2H, J = 12.6 Hz), 4.18 (t, 2H, J = 5.0 Hz), 6.80 - 6.83 (m, 2H), 7.02 (d, 2H, J = 8.8 Hz), 7.12 (d, 1H, J = 8.0 Hz), 7.29 - 7.41 (m, 4H), 7.51 - 7.60 (m, 6H), 7.74 (d, 1H, J = 2.2, Hz).

Anal. Calcd. C<sub>41</sub>H<sub>47</sub>N<sub>3</sub>O<sub>5</sub>S·0.2H<sub>2</sub>O Calcd. C, 70.60; H, 6.85; N, 6.02. Found C, 70.46; H, 6.89; N, 5.97.

#### Working Example 79 (Production of Compound 79)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-[(1-ethylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (150mg) in dichloromethane(10ml). Then, thionyl chloride (47mg) was added at 0°C, the temperature was returned to room temperature, and the mixture was stirred under nitrogen atmosphere for 1 hour. Then, this solution was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (88mg) and triethylamine (805mg) in dichloromethane (20ml) at 0°C. The mixture was stirred under nitrogen atmosphere at room temperature



overnight, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 3), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(1-ethylpyrazol-4-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 79) (99mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.34 - 1.85 (m, 11H), 2.21 (s, 3H), 2.64 (br, 1H), 2.84 (br, 2H), 3.29 - 3.46 (m, 4H), 3.52 - 3.59 (m, 4H), 3.80 (t, 2H, J = 4.4 Hz), 4.04 (d, 2H, J = 9.4 Hz), 4.11 - 4.18 (m, 4H), 4.44 (s, 2H), 6.96 - 7.01 (m, 3H), 7.28 - 7.36 (m, 3H), 7.40 - 7.56 (m, 9H).

Anal. Calcd. C<sub>42</sub>H<sub>53</sub>N<sub>5</sub>O<sub>4</sub> Calcd. C, 72.91; H, 7.72; N, 10.12. Found C, 72.69; H, 8.00; N, 9.92.

#### Working Example 80 (Production of Compound 80)

One droplet of DMF was added to a solution of 2-methyldioxolane-2-ylacetic acid in tetrahydrofuran (10ml). Then, thionyl chloride (80mg) was added at 0°C, the temperature was returned to room temperature, and the

1003331-121201

mixture was stirred under nitrogen atmosphere for 1 hour. This solution was added to a solution of 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (100mg) and pyridine (528mg) in tetrahydrofuran (20ml) at 0°C. The mixture was stirred under nitrogen atmosphere at room temperature overnight, the insolubles were filtered off using Celite, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 3), which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[2-(2-methyl-1,3-dioxolan-2-yl)acetyl]-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 80) (60mg) as colorless crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.0 Hz), 1.34 - 1.85 (m, 11H), 2.21 (s, 3H), 2.50 - 3.05 (m, 5H), 3.20 (d, 1H, J = 13.6 Hz), 3.38 (td, 2H, J = 10.8, 3.6 Hz), 3.53 - 3.70 (m, 5H), 3.75 - 3.95 (m, 5H), 4.04 (d, 2H, J = 10.2 Hz), 4.18 (t, 2H, J = 5.4 Hz), 4.90 (d, 1H, J = 13.2 Hz), 7.03 (d, 2H, J = 9.2 Hz), 7.29 - 7.35 (m, 3H), 7.51 - 7.67

(m, 8H).

Anal. Calcd.  $C_{42}H_{53}N_3O_7 \cdot 0.1H_2O$  Calcd. C, 70.68; H, 7.51; N, 5.89. Found C, 70.41; H, 7.33; N, 5.89.

Working Example 81 (Production of Compound 81)

5 A catalytic amount of N,N-dimethyl-4-aminopyridine was added to a solution of 7-(4-butoxyethoxyphenyl)-1-  
 10 [(4-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (150mg), 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (88mg) and 1-  
 15 hydroxybenzotriazole (96mg) in DMF (15ml), followed by addition of 1-ethyl-3-(3-dimethylaminopropylcarbodiimide (137mg). The mixture was stirred under nitrogen atmosphere at room temperature overnight. To the mixture was added water, and the mixture was extracted with ethyl  
 20 acetated. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 3) to give  
 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-1-[(4-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 81) (7mg) as yellow amorphous.  
 25  $^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  0.93 (t, 3H, J = 7.2 Hz), 1.34 - 1.47 (m, 2H), 1.51 - 1.80 (m, 6H), 2.21 (s, 3H), 2.52 (s,

Amen.  
B45

10018321-121201

3H), 2.63 (br, 1H), 2.84 (br, 2H), 3.33 - 3.42 (m, 4H),  
3.52 - 3.59 (m, 4H), 3.81 (t, 2H, J = 4.4 Hz), 4.04 (d, 2H,  
J = 12.2 Hz), 4.16 (t, 2H, J = 4.8 Hz), 4.67 (s, 2H), 6.95  
(d, 1H, J = 6.2 Hz), 6.99 (d, 2H, J = 7.0 Hz), 7.30 (d, 2H,  
5 J = 8.8 Hz), 7.40 - 7.56 (m, 8H), 8.68 (s, 1H).

Working Example 82 (Production of Compound 82)

One droplet of DMF was added to a solution of 7-(4-butoxyethoxyphenyl)-1-[(1-isopropylpyrazol-4-yl)methyl]-  
2,3-dihydro-1-benzazepine-4-carboxylic acid (150mg) in  
10 dichloromethane (10ml). Then, thionyl chloride (49mg)  
was added at 0°C, the temperature was returned to room  
temperature, and the mixture was stirred under nitrogen  
atmosphere for 1 hour. Then, this solution was added to  
a solution of 4-[[N-methyl-N-(tetrahydropyran-4-  
15 yl)amino]methyl]aniline (90mg) and triethylamine (830mg)  
in dichloromethane (20ml) at 0°C. The mixture was  
stirred under nitrogen atmosphere at room temperature  
overnight, to the mixture was added water, and the  
mixture was extracted with ethyl acetate. The organic  
20 layer was washed with saturated brine and dried with  
magnesium sulfate. The solvent was evaporated under  
reduced pressure, and the resulting residue was separated  
and purified with silica gel column chromatography  
(methanol : ethyl acetate = 1 : 3), which was  
25 recrystallized to give 7-(4-butoxyethoxyphenyl)-1-[(1-

isopropylpyrazol-4-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 82) (119mg) as yellow crystals.

- 5 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 - 1.85 (m, 14H), 2.21 (s, 3H), 2.65 (br, 1H), 2.84 (br, 2H), 3.36 - 3.52 (m, 4H), 3.56 - 3.59 (m, 4H), 3.81 (t, 2H, J = 4.4 Hz), 4.04 (d, 2H, J = 11.8 Hz), 4.16 (t, 2H, J = 5.0 Hz), 4.44 - 4.52 (m, 3H), 6.96 - 7.02 (m, 3H), 7.30 (d, 2H, J = 8.6 Hz), 7.39 - 7.56 (m, 10H).
- 10 Anal. Calcd. C<sub>43</sub>H<sub>55</sub>N<sub>5</sub>O<sub>4</sub>. Calcd. C, 73.16; H, 7.85; N, 9.92. Found C, 72.99; H, 7.76; N, 9.75.

#### Reference Example 147

- To a suspension of 60% sodium hydride (0.17g) in DMF
- 15 (5ml) which had been washed with hexane three times was added dropwise a solution of methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (1.0g) in DMF (10ml) at 0°C under nitrogen atmosphere. The temperature was returned to room temperature and the mixture was stirred for 1
- 20 hour. Then, a solution of allyl bromide (0.56g) in DMF (5ml) was added dropwise thereto at 0°C, the temperature was returned to room temperature, and the mixture was stirred at room temperature overnight. To the mixture were added ethyl acetate and water, and the mixture was
- 25 separated. The organic layer was washed with saturated

brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 7 : 1) to give  
5 methyl 1-allyl-7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (0.38g) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.79 (t, 2H, J = 5.4 Hz), 3.22 (t, 2H, J = 5.2 Hz), 3.80 (s, 3H), 3.89 (d, 2H, J = 4.8 Hz), 5.16 - 5.28 (m, 2H), 5.81 - 5.97 (m, 1H), 6.58 (d, 1H, J =  
10 8.8 Hz), 7.23 (dd, 1H, J = 8.8, 2.6 Hz), 7.4 (d, 1H, J = 2.6 Hz), 7.59 (s, 1H).

#### Reference Example 148

In toluene (20ml), ethanol (2ml) and water (2ml) were suspended methyl 1-allyl-7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (274mg), 4-propoxyethoxyphenyl  
15 borate (248mg) and potassium carbonate (307mg), and the suspension was stirred under argon atmosphere for 30 minutes. Then, tetrakis(triphenylphosphine)palladium (69mg) was added thereto, and the mixture was heated  
20 under argon atmosphere at 100°C for 8 hours. After allowing to cool, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under  
25 reduced pressure and the resulting residue was purified

with silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give methyl 1-allyl-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (269mg) as yellow oil.

5 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.8 Hz), 1.58 - 1.75 (m, 2H), 2.81 (t, 2H, J = 5.6 Hz), 3.27 (t, 2H, J = 4.4 Hz), 3.51 (t, 2H, J = 6.6 Hz), 3.75 - 3.83 (m, 5H), 3.96 (d, 2H, J = 5.2 Hz), 4.16 (t, 2H, J = 4.8 Hz), 5.23 - 5.30 (m, 2H), 5.88 - 6.02 (m, 1H), 6.87 (d, 1H, J = 8.8 Hz),  
10 6.97 (d, 2H, J = 8.4 Hz), 7.39 (dd, 1H, J = 8.8, 2.2 Hz), 7.46 (d, 2H, J = 8.4 Hz), 7.52 (d, 1H, J = 2.2 Hz), 7.78 (s, 1H).

#### Reference Example 149

To a solution of methyl 1-allyl-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (262mg) in a mixture of tetrahydrofuran  
15 (19ml) and methanol (19ml) was added 1N sodium hydroxide solution (6.3ml), and the mixture was stirred at room temperature overnight. Then, water and 1N hydrochloric  
20 acid were added to make acidic (pH = 4) at 0°C, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give the solid, which was washed with  
25 hexane to give 1-allyl-7-(4-propoxyethoxyphenyl)-2,3-

dihydro-1-benzazepine-4-carboxylic acid (199mg) as yellow crystals.

mp 152.0 - 153.0°C

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.4 Hz), 1.56 -  
5 1.74 (m, 2H), 3.00 (t, 2H, J = 5.2 Hz), 3.30 (t, 2H, J =  
5.2 Hz), 3.51 (t, 2H, J = 6.4 Hz), 3.81 (t, 2H, J = 5.0 Hz),  
3.97 (d, 2H, J = 5.2 Hz), 4.16 (t, 2H, J = 4.8 Hz), 5.24 -  
5.30 (m, 2H), 5.89 - 6.10 (m, 1H), 6.88 (d, 1H, J = 8.4 Hz),  
6.98 (d, 2H, J = 8.4 Hz), 7.40 - 7.49 (m, 3H), 7.53 (d, 1H,  
10 J = 2.6 Hz), 7.88 (s, 1H).

Anal. Calcd. C<sub>25</sub>H<sub>29</sub>NO<sub>4</sub> · 0.1H<sub>2</sub>O Calcd. C, 73.36; H, 7.19; N,  
3.42. Found C, 73.11; H, 7.09; N, 3.25.

#### Reference Example 150

To a suspension of 60% sodium hydride (0.23g) in  
15 tetrahydrofuran (5ml) which had been washed with hexane  
three times was added dropwise a solution of methyl 7-  
bromo-2,3-dihydro-1-benzazepine-4-carboxylate (0.80g) in  
tetrahydrofuran (10ml) at 0°C under nitrogen atmosphere.  
The temperature was returned to room temperature and the  
20 mixture was stirred for 30 minutes. Then, a solution of  
allyl bromide (5.12g) in tetrahydrofuran (5ml) was added  
dropwise thereto at 0°C, and the mixture was stirred at  
60°C for 5 days. To the mixture were added ethyl acetate  
and water, and the mixture was separated. The organic  
25 layer was washed with saturated brine and dried with



magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to give allyl 1-allyl-7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (0.22g) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.81 (t, 2H, J = 5.8 Hz), 3.23 (t, 2H, J = 5.2 Hz), 3.90 (d, 2H, J = 4.8 Hz), 4.69 - 4.73 (m, 2H), 5.11 - 5.42 (m, 4H), 5.81 - 6.07 (m, 2H), 6.68 (d, 1H, J = 9.2 Hz), 7.23 (dd, 1H, J = 8.8, 2.2 Hz), 7.43 (d, 1H, J = 2.4 Hz), 7.62 (s, 1H).

#### Reference Example 151

To a solution of allyl 1-allyl-7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (224mg) in tetrahydrofuran (10ml) were added tetrakis(triphenylphosphine)palladium (74mg) and morpholine (560mg), and the mixture was stirred under argon atmosphere at room temperature for 2 hours. To the mixture was added water at 0°C, and the mixture was made acidic (pH = 4) with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid, further with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give 1-allyl-7-bromo-2,3-dihydro-1-benzazepine-4-carboxylic acid (198mg) as yellow amorphous.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.80 (t, 2H, J = 4.2 Hz), 3.23 (t,

2H,  $J = 4.8$  Hz), 3.91 (d, 2H,  $J = 4.8$  Hz), 5.17 - 5.28 (m, 2H), 5.84 - 5.98 (m, 1H), 6.69 (d, 1H,  $J = 9.2$  Hz), 7.24 (dd, 1H,  $J = 8.8, 2.2$  Hz), 7.43 - 7.73 (m, 2H).

Reference Example 152

5        1-allyl-7-bromo-2,3-dihydro-1-benzazepine-4-carboxylic acid (320mg) was dissolved in tetrahydrofuran (15 ml), and DMF (0.3ml) was added to the solution. Then, thionyl chloride (0.23ml) was added thereto at 0°C, and the mixture was stirred under nitrogen atmosphere at room  
10        temperature for 2 hours. The solvent and excess thionyl chloride were evaporated under reduced pressure, and the resulting residue was suspended in tetrahydrofuran (25ml), and the suspension was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline  
15        (275mg) and triethylamine (1.27g) in tetrahydrofuran (10ml) at 0°C. The temperature was returned to room temperature, and the mixture was stirred overnight. To the mixture was added water, and the mixture was extracted with ethyl acetate twice. The organic layer  
20        was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was separated and purified with silica gel column chromatography (methanol : ethyl acetate = 1 : 8) to give 1-allyl-7-bromo-N-[4-[[N-methyl-N-(tetrahydropyran-4-

25

yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (266mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.75 (br, 4H), 2.21 (s, 3H), 2.65 (br, 1H), 2.88 (t, 2H, J = 4.4 Hz), 3.29 (t, 2H, J = 5.0 Hz), 3.37 (dt, 2H, J = 8.2, 2.4 Hz), 3.57 (s, 2H), 3.92 (d, 2H, J = 4.8 Hz), 4.04 (d, 2H, J = 11.8 Hz), 5.20 - 5.30 (m, 2H), 5.85 - 5.96 (m, 1H), 6.72 (d, 1H, J = 9.2 Hz), 7.22 - 7.32 (m, 3H), 7.42 - 7.54 (m, 4H).

Reference Example 153

10 To a solution of methyl 7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 2-methoxybenzaldehyde (535mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxyborohydride (749mg), and the mixture was stirred under nitrogen atmosphere at room  
15 temperature overnight. Then, water was added thereto and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified  
20 with silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give methyl (1-(2-methoxybenzyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (394mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.6 Hz), 1.58 - 1.70 (m, 2H), 2.82 (br, 2H), 3.35 (br, 2H), 3.51 (t, 2H, J

Ammon  
B46  
100-6321-121201

= 6.6 Hz), 3.78 - 3.94 (m, 8H), 4.16 (t, 2H, J = 4.6 Hz), 4.57 (s, 2H), 6.78 (d, 1H, J = 9.2 Hz), 6.88 - 6.99 (m, 4H), 7.15 (d, 1H, J = 8.0 Hz), 7.26 - 7.44 (m, 2H), 7.46 (d, 2H, J = 8.4 Hz), 7.55 (d, 1H, J = 2.4 Hz), 7.84 (s, 1H).

5           Reference Example 154

10           To a solution of methyl 1-(2-methoxybenzyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (394mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 1 day. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was recrystallized from hexane-ethyl acetate to give 1-(2-methoxybenzyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (217mg) as yellow crystals.

20           <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.2 Hz), 1.59 - 1.70 (m, 2H), 2.84 (br, 2H), 3.37 (br, 2H), 3.51 (t, 2H, J = 6.6 Hz), 3.81 (t, 2H, J = 4.8 Hz), 3.89 (s, 3H), 4.16 (t, 2H, J = 5.2 Hz), 4.58 (s, 2H, ), 6.80 (d, 1H, J = 8.8 Hz), 6.91 - 7.00 (m, 4H), 7.14 (d, 1H, J = 6.6 Hz), 7.29 - 7.36

(m, 2H), 7.46 (d, 2H, J = 8.8 Hz), 7.55 (d, 1H, J = 2.4 Hz), 7.94 (s, 1H).

Anal. Calcd.  $C_{30}H_{33}NO_5$  Calcd. C, 73.90; H, 6.82; N, 2.87.

Found C, 73.58; H, 6.66; N, 2.76.

5           Reference of Example 155

10           To a solution of methyl 7-(4-butoxyethoxyphenyl)-  
2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 2-  
methoxybenzaldehyde (517mg) in 1,2-dichloroethane (10ml)  
was added sodium triacetoxymethylborohydride (724mg), and the  
mixture was stirred under nitrogen atmosphere at room  
temperature overnight. Then, water was added to the  
mixture, and the mixture was extracted with ethyl acetate.  
The organic layer was washed with saturated brine and  
dried with magnesium sulfate. The solvent was evaporated  
15           under reduced pressure, and the resulting residue was  
purified with silica gel column chromatography (hexane :  
ethyl acetate = 3 : 1) to give methyl 7-(4-  
butoxyethoxyphenyl)-1-(2-methoxybenzyl)-2,3-dihydro-1-  
benzazepine-4-carboxylate (391mg) as yellow oil.  
20            $^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  0.93 (t, 3H, J = 7.4 Hz), 1.37 -  
1.45 (m, 2H), 1.55 - 1.64 (m, 2H), 2.82 (br, 2H), 3.35 (br,  
2H), 3.55 (t, 2H, J = 6.6 Hz), 3.78 - 3.82 (m, 5H), 3.88 (s,  
3H), 4.16 (t, 2H, J = 5.6 Hz), 4.57 (s, 2H), 6.78 (d, 1H, J  
= 8.4 Hz), 6.91 - 6.99 (m, 4H), 7.14 (d, 1H, J = 6.4 Hz),  
25           7.26 - 7.40 (m, 2H), 7.46 (d, 2H, J = 8.8 Hz), 7.54 (d, 1H,

J = 2.4 Hz), 7.84 (s, 1H).

Reference Example 156

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-(2-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (391mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 1 day. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (257mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.34 - 1.45 (m, 2H), 1.57 - 1.64 (m, 2H), 2.84 (br, 2H), 3.36 (br, 2H), 3.55 (t, 2H, J = 6.6 Hz), 3.80 (t, 2H, J = 4.8 Hz), 3.88 (s, 3H), 4.15 (t, 2H, J = 5.2 Hz), 4.58 (s, 2H), 6.79 (d, 1H, J = 9.2 Hz), 6.91 - 6.99 (m, 4H), 7.14 (d, 1H, J = 7.4 Hz), 7.29 - 7.36 (m, 2H), 7.46 (d, 2H, J = 8.8 Hz), 7.55 (d, 1H, J = 2.4 Hz), 7.94 (s, 1H).

Anal. Calcd. C<sub>31</sub>H<sub>35</sub>NO<sub>5</sub> Calcd. C, 74.23; H, 7.03; N, 2.79.

Found C, 73.96; H, 6.91; N, 2.75.

~~Reference Example 157~~

Ammon.  
47

To a suspension of 60% sodium hydride (0.23g) in tetrahydrofuran (5ml) which had been washed with hexane three times was added dropwise a solution of methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (0.80g) in tetrahydrofuran (10ml) under nitrogen atmosphere at 0°C. The temperature was returned to room temperature and the mixture was stirred for 1 hour. Then, to the mixture was added dropwise a solution of 3-methoxybenzyl bromide (2.29g) in tetrahydrofuran (5ml) at 0°C. The temperature was returned to room temperature, and the mixture was stirred for 3 days. To the mixture were added ethyl acetate and water, and the mixture was separated. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to give methyl 7-bromo-1-(3-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.69g) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.76 (t, 2H, J = 5.8 Hz), 3.26 (t, 2H, J = 3.8 Hz), 3.79 - 3.81 (m, 6H), 4.49 (s, 2H), 6.67 (d, 1H, J = 8.8 Hz), 6.78 - 6.93 (m, 3H), 7.17 - 7.31 (m, 2H), 7.46 (d, 1H, J = 2.2 Hz), 7.63 (z, 1H).

## Reference Example 158

To a solution of methyl 7-bromo-1-(3-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (691mg) in a mixture of tetrahydrofuran (50ml) and methanol (50ml) was added 1N sodium hydroxide solution (17ml), and the mixture was stirred at room temperature for 3 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was recrystallized from hexane-ethyl acetate to give 7-bromo-1-(3-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (369mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.78 (t, 2H, J = 5.6 Hz), 3.29 (t, 2H, J = 5.6 Hz), 3.79 (s, 3H), 4.51 (s, 2H), 6.68 (d, 1H, J = 9.2 Hz), 6.78 - 6.84 (m, 3H), 7.20 - 7.32 (m, 2H), 7.48 (d, 1H, J = 2.6 Hz), 7.73 (s, 1H).

Anal. Calcd. C<sub>19</sub>H<sub>18</sub>NO<sub>3</sub>Br Calcd. C, 58.78; H, 4.67; N, 3.61. Found C, 58.81; H, 4.68; N, 3.61.

## Reference Example 159

In toluene (20ml), ethanol (2ml) and water (2ml) were suspended 7-bromo-1-(3-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (300mg), 4-



propoxyethoxyphenyl borate (346mg) and potassium carbonate (534mg), and the suspension was stirred under argon atmosphere for 30 minutes. Then, to the suspension was added tetrakis(triphenylphosphine)palladium (62mg), and  
5 the mixture was heated at 100°C for 6 hours under argon atmosphere. After allowing to cool, water was added to the mixture, which was made acidic (pH=4) with 1N hydrochloric acid and extracted with ethyl acetate twice. The organic layer was washed with water and saturated  
10 brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and the resulting solid was recrystallized from hexane-ethyl acetate to give 1-  
15 (3-methoxybenzyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (118mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.4 Hz), 1.60 - 1.70 (m, 2H), 2.81 (br, 2H), 3.34 (br, 2H), 3.51 (t, 2H, J = 7.0 Hz), 3.80 - 3.84 (m, 5H), 4.16 (t, 2H, J = 5.0 Hz), 4.58 (s, 2H), 6.85 - 6.90 (m, 4H), 6.98 (d, 2H, J = 8.8 Hz), 7.26 - 7.45 (m, 2H), 7.47 (d, 2H, J = 8.4 Hz), 7.56 (d, 1H, J = 2.4 Hz), 7.93 (s, 1H).

#### Reference Example 160

25 In toluene (15ml), ethanol (1.5ml) and water (1.5ml)

were suspended 7-bromo-1-(3-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (320mg), 4-butoxyethoxyphenyl borate (246mg) and potassium carbonate (285mg), and the suspension was stirred under argon

5 atmosphere for 30 minutes. Then, to the suspension was added tetrakis(triphenylphosphine)palladium (64mg), and the mixture was heated at 100°C for 8 hours under argon atmosphere. After allowing to cool, water was added to the mixture, and the mixture was extracted with ethyl  
10 acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to give  
15 methyl 7-(4-butoxyethoxyphenyl)-1-(3-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (207mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.30 - 1.50 (m, 2H), 1.55 - 1.65 (m, 2H), 2.78 (t, 2H, J = 4.8 Hz),  
20 3.31 (t, 2H, J = 4.8 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.78 - 3.82 (m, 8H), 4.16 (t, 2H, J = 5.0 Hz), 4.56 (s, 2H), 6.77 - 6.90 (m, 4H), 6.97 (d, 2H, J = 8.6 Hz), 7.24 - 7.29 (m, 1H), 7.36 (dd, 1H, J = 8.4, 2.2 Hz), 7.46 (d, 2H, J = 9.2 Hz), 7.55 (d, 1H, J = 2.2 Hz), 7.82 (s, 1H).

25 Reference Example 161

To a solution of 7-bromo-1-(2-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (202mg) in a mixture of tetrahydrofuran (13ml) and methanol (13ml) was added 1N sodium hydroxide solution (4ml), and the mixture was stirred at room temperature for 3 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(3-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (161mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 - 1.45 (m, 2H), 1.54 - 1.65 (m, 2H), 2.81 (br, 2H), 3.34 (br, 2H), 3.55 (t, 2H, J = 6.6 Hz), 3.78 - 3.83 (m, 5H), 4.16 (t, 2H, J = 5.2 Hz), 4.58 (s, 2H), 6.82 - 6.90 (m, 4H), 6.98 (d, 2H, J = 8.8 Hz), 7.29 - 7.41 (m, 2H), 7.46 (d, 2H, J = 8.8 Hz), 7.56 (d, 1H, J = 2.4 Hz), 7.93 (s, 1H).

#### Reference Example 162

To a suspension of 60% sodium hydride (0.16g) in DMF (5ml) which had been washed with hexane three times was added dropwise a solution of methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (1.00g) in DMF (10ml) under

nitrogen atmosphere at 0°C. The temperature was returned to room temperature and the mixture was stirred for 1 hour. Then, to the mixture was added dropwise a solution of 4-methoxybenzyl bromide (0.67g) in DMF (5ml) at 0°C.

- 5 To the mixture was added sodium iodide (0.83g), and the mixture was heated at 60°C overnight. To the mixture were added ethyl acetate and water, and the mixture was separated. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was
- 10 evaporated under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to give methyl 7-bromo-1-(4-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.92g) as yellow oil.
- 15 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.72 (t, 2H, J = 4.4 Hz), 3.23 (t, 2H, J = 5.0 Hz), 3.80 - 3.82 (m, 6H), 4.46 (s, 2H), 6.70 (d, 1H, J = 4.6 Hz), 6.90 (d, 2H, J = 8.4 Hz), 7.22 - 7.29 (m, 1H), 7.46 (d, 1H, J = 2.2 Hz), 7.62 (s, 1H).

#### Reference Example 163

- 20 To a solution of methyl 7-bromo-1-(4-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (920mg) in a mixture of tetrahydrofuran (70ml) and methanol (70ml) was added 1N sodium hydroxide solution (23ml), and the mixture was stirred at room temperature for 1 day. Then,
- 25 to the mixture was added water at 0°C, and 1N

hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was recrystallized from hexane-ethyl acetate to give 7-bromo-1-(4-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (644mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.74 (t, 2H, J = 4.4 Hz), 3.26 (t, 2H, J = 4.4 Hz), 3.82 (s, 3H), 4.48 (s, 2H), 6.71 (d, 1H, J = 8.8 Hz), 6.89 (s, 2H), 7.16 (d, 2H, J = 8.4 Hz), 7.23 (dd, 1H, J = 8.8, 2.6 Hz), 7.48 (d, 1H, J = 2.6 Hz), 7.73 (s, 1H).

Anal. Calcd. C<sub>19</sub>H<sub>18</sub>NO<sub>3</sub>Br Calcd. C, 58.78; H, 4.67; N, 3.61. Found C, 58.60; H, 4.61; N, 3.57.

#### Reference Example 164

In toluene (20ml), ethanol (2ml) and water (2ml) were suspended 7-bromo-1-(4-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (300mg), 4-propoxyethoxyphenyl borate (346mg) and potassium carbonate (534mg), and the suspension was stirred under argon atmosphere for 30 minutes. Then, to the suspension was added tetrakis(triphenylphosphine)palladium (63mg), and the mixture was heated at 100°C for 4 hours under argon atmosphere. After allowing to cool, water was added to

the mixture, which was made acidic (pH = 4) with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was  
5 evaporated under reduced pressure, the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 1 : 1) and the resulting solid was recrystallized from hexane-ethyl acetate to give 1-(4-methoxybenzyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-  
10 1-benzazepine-4-carboxylic acid (117mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.2 Hz), 1.60 - 1.70 (m, 2H), 2.76 (br, 2H), 3.31 (br, 2H), 3.51 (t, 2H, J = 7.0 Hz), 3.79 - 3.84 (m, 5H), 4.16 (t, 2H, J = 4.6 Hz),  
15 4.54 (s, 2H), 6.88 - 7.00 (m, 5H), 7.22 (d, 2H, J = 8.8 Hz), 7.39 (d, 1H, J = 10.6 Hz), 7.47 (d, 2H, J = 8.4 Hz), 7.56 (d, 1H, J = 2.2 Hz), 7.92 (s, 1H).

#### Reference Example 165

In toluene (20ml), ethanol (2ml) and water (2ml)  
20 were suspended 7-bromo-1-(4-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (300mg), 4-butoxyethoxyphenyl borate (368mg) and potassium carbonate (534mg), and the suspension was stirred under argon atmosphere for 30 minutes. Then, to the suspension was  
25 added tetrakis(triphenylphosphine)palladium (63mg), and the

mixture was heated at 100°C for 6 hours under argon atmosphere. After allowing to cool, water was added to the mixture, which was made acidic (pH = 4) with 1N hydrochloric acid and extracted with ethyl acetate twice.

- 5 The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and the resulting solid
- 10 was washed with hexane to give 7-(4-butoxyethoxyphenyl)-1-(4-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (149mg) as yellow crystals.
- <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.25 - 1.41 (m, 2H), 1.58 - 1.65 (m, 2H), 2.76 (br, 2H), 3.31 (br, 2H), 3.56 (t, 2H, J = 7.0 Hz), 3.78 - 3.82 (m, 5H), 4.16 (t, 2H, J = 5.4 Hz), 4.54 (s, 2H), 6.88 - 7.000 (m, 5H), 7.22 (d, 2H, J = 8.4 Hz), 7.39 (dd, 1H, J = 10.2, 2.4 Hz), 7.47 (d, 2H, J = 8.8 Hz), 7.57 (d, 1H, J = 2.4 Hz), 7.92 (s, 1H).
- 15 Anal. Calcd. C<sub>31</sub>H<sub>35</sub>NO<sub>5</sub> Calcd. C, 74.23; H, 7.03; N, 2.79.
- 20 Found C, 73.88; H, 6.78; N, 2.85.

#### Reference Example 166

- To a solution of methyl 7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 3-thiophenecarboxyaldehyde (441mg) in 1,2-dichloroethane
- 25 (10ml) was added sodium triacetoxymethylborohydride (416mg),

and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and  
5 dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give methyl 7-(4-propoxyethoxyphenyl)-1-(3-thienylmethyl)-2,3-dihydro-1-  
10 benzazepine-4-carboxylate (375mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.4 Hz), 1.60 - 1.70 (m, 2H), 2.76 (t, 2H, J = 3.6 Hz), 3.31 (t, 2H, J = 3.6 Hz), 3.51 (t, 2H, J = 6.6 Hz), 3.79 - 3.83 (m, 5H), 4.16 (t, 2H, J = 5.2 Hz), 4.56 (s, 2H), 6.90 - 7.04 (m, 4H),  
15 7.12 - 7.14 (m, 1H), 7.32 - 7.45 (m, 2H), 7.47 (d, 2H, J = 8.6 Hz), 7.55 (d, 1H, J = 2.2 Hz), 7.81 (s, 1H).

#### Reference Example 167

To a solution of methyl 7-(4-propoxyethoxyphenyl)-1-(3-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate  
20 (375mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature overnight. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic  
25 (pH = 4), and the mixture was extracted with ethyl



acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was recrystallized from hexane-ethyl acetate to give 7-(4-propoxyethoxyphenyl)-1-(3-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (317mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.4 Hz), 1.56 - 1.74 (m, 2H), 2.78 (t, 2H, J = 4.4 Hz), 3.51 (t, 2H, J = 6.8 Hz), 3.81 (t, 2H, J = 4.4 Hz), 4.17 (t, 2H, J = 5.2 Hz), 4.58 (s, 2H), 6.91 - 7.05 (m, 4H), 7.13 (br, 1H), 7.33 - 7.49 (m, 4H), 7.56 (d, 1H, J = 2.2 Hz), 7.91 (s, 1H).

Anal. Calcd. C<sub>27</sub>H<sub>29</sub>NO<sub>4</sub>S Calcd. C, 69.95; H, 6.31; N, 3.02. Found C, 69.78; H, 6.30; N, 3.01.

#### Reference Example 168

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 3-thiophenecarboxyaldehyde (426mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxymethylborohydride (402mg), and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was

purified with silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give methyl 7-(4-butoxyethoxyphenyl)-1-(3-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (373mg) as yellow oil.

5 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.25 - 1.45 (m, 2H), 1.57 - 1.65 (m, 2H), 2.76 (t, 2H, J = 3.6 Hz), 3.31 (t, 2H, J = 4.6 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.78 - 3.83 (m, 5H), 4.16 (t, 2H, J = 5.2 Hz), 4.56 (s, 2H), 6.90 - 7.13 (m, 5H), 7.32 - 7.41 (m, 2H), 7.47 (d, 2H, J = 8.8  
10 Hz), 7.55 (s, 1H), 7.81 (s, 1H).

Reference Example 169

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-(3-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (373mg) in a mixture of tetrahydrofuran (24ml) and  
15 methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 3 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl  
20 acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(3-  
25 thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic

acid (297mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 - 1.45 (m, 2H), 1.57 - 1.65 (m, 2H), 2.78 (t, 2H, J = 4.0 Hz), 3.29 (t, 2H, J = 4.0 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.80 (t, 2H, J = 4.8 Hz), 4.16 (t, 2H, J = 5.2 Hz), 4.57 (s, 2H), 6.73 - 7.00 (m, 3H), 7.03 (dd, 1H, J = 5.0, 1.4 Hz), 7.33 - 7.49 (m, 4H), 7.56 (d, 1H, J = 1.8 Hz), 7.90 (s, 1H).

Anal. Calcd. C<sub>28</sub>H<sub>31</sub>NO<sub>4</sub>S · 0.1H<sub>2</sub>O Calcd. C, 70.14; H, 6.56; N, 2.92. Found C, 69.85; H, 6.46; N, 2.86.

10        Reference Example 170

One droplet of pyridine was added to a solution of 2-hydroxymethylthiophene (1.0g) in toluene (10ml), followed by addition of thionyl chloride (1.56g). The mixture was stirred at room temperature for 1 hour, ethyl acetate was added thereto, and the mixture was washed with water. The organic layer was washed with 1N sodium hydroxide solution, water and saturated brine, and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give 2-chloromethylthiophene (1.16g) as deep brown oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 4.82 (s, 2H), 6.93 - 7.00 (m, 1H), 7.09 (d, 1H, J = 3.0 Hz), 7.31 (dd, 1H, J = 5.2, 1.0 Hz).

Reference Example 171

To a suspension of 60% sodium hydride (0.16g) in DMF (5ml) which had been washed with hexane three times was

added dropwise a solution of methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (1.00g) in DMF (10ml) under nitrogen atmosphere at 0°C. The temperature was returned to room temperature and the mixture was stirred for 1 hour. Then, to the mixture was added dropwise a solution of 2-chloromethylthiophene (1.07g) in DMF (5ml) at 0°C. To the mixture was added sodium iodide (0.83g), and the mixture was heated at 60°C overnight. To the mixture were added ethyl acetate and water, and the mixture was separated. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 5 : 1) to give methyl 7-bromo-1-(2-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.82g) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.78 (t, 2H, J = 3.6 Hz), 3.27 (t, 2H, J = 3.6 Hz), 3.80 (s, 3H), 4.65 (s, 2H), 6.82 (d, 1H, J = 7.8 Hz), 6.70 - 7.03 (m, 2H), 7.24 - 7.35 (m, 2H), 7.47 (d, 1H, J = 2.8 Hz), 7.61 (s, 1H).

#### Reference Example 172

To a solution of methyl 7-bromo-1-(2-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (810mg) in a mixture of tetrahydrofuran (60ml) and methanol (60ml) was added 1N sodium hydroxide solution (21ml), and the

mixture was stirred at room temperature overnight. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate.

- 5 The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was recrystallized from hexane-ethyl acetate to give 7-bromo-1-(2-thienylmethyl)-2,3-dihydro-1-
- 10 benzazepine-4-carboxylic acid (574mg) as yellow crystals. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.79 (t, 2H, J = 4.4 Hz), 3.30 (t, 2H, J = 4.8 Hz), 4.66 (s, 2H), 6.83 (d, 1H, J = 4.4 Hz), 6.97 - 7.01 (m, 2H), 7.24 - 7.49 (m, 21H), 7.48 (d, 1H, J = 2.4 Hz), 7.71 (s, 1H).
- 15 Anal. Calcd. C<sub>16</sub>H<sub>14</sub>NO<sub>2</sub>SBr Calcd. C, 52.76; H, 3.87; N, 3.85. Found C, 52.80; H, 3.95; N, 3.68.

#### Reference Example 173

- In toluene (30ml), ethanol (3ml) and water (3ml) were suspended 7-bromo-1-(2-thienylmethyl)-2,3-dihydro-1-
- 20 benzazepine-4-carboxylic acid (500mg), 4-propoxyethoxyphenyl borate (615mg) and potassium carbonate (949mg), and the suspension was stirred under argon atmosphere for 30 minutes. Then, to the suspension was added tetrakis(triphenylphosphine)palladium (111mg),
- 25 and the mixture was heated under argon atmosphere at

100°C for 6 hours. After allowing to cool, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 1 : 1), which was recrystallized from hexane-ethyl acetate to give 7-(4-propoxyethoxyphenyl)-1-(2-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (269mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.6 Hz), 1.59 - 1.74 (m, 2H), 2.79 (br, 2H), 3.30 (br, 2H), 3.51 (t, 2H, J = 6.6 Hz), 3.81 (t, 2H, J = 5.0 Hz), 4.15 (br, 2H), 4.68 (br, 2H), 6.90 - 7.10 (m, 5H), 7.23 - 7.26 (m, 1H), 7.43 - 7.47 (m, 3H), 7.54 (br, 1H), 7.90 (s, 1H).

Anal. Calcd. C<sub>27</sub>H<sub>29</sub>NO<sub>4</sub>S·0.2H<sub>2</sub>O Calcd. C, 69.41; H, 6.34; N, 3.00. Found C, 69.18; H, 6.05; N, 3.01.

#### Reference Example 174

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and thiophene-2-carboxyaldehyde (422mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxymethylborohydride (796mg), and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate.

The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane :

5 ethyl acetate = 3 : 1) to give methyl 7-(4-butoxyethoxyphenyl)-1-(2-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (373mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.30 - 1.47 (m, 2H), 1.56 - 1.71 (m, 2H), 2.80 (t, 2H, J = 5.4 Hz),  
10 3.32 (t, 2H, J = 5.4 Hz), 3.55 (t, 2H, J = 7.0 Hz), 3.78 - 3.83 (m, 5H), 4.16 (t, 2H, J = 5.0 Hz), 4.71 (s, 2H), 6.96 - 7.02 (m, 5H), 7.29 (dd, 1H, J = 4.8, 1.4 Hz), 7.40 - 7.49 (m, 3H), 7.55 (d, 1H, J = 2.2 Hz), 7.80 (s, 1H).

#### Reference Example 175

15 To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-(3-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (373mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature  
20 for 1 day. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The  
25 solvent was evaporated under reduced pressure, and the

10018331.121201

resulting solid was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2-thienylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (249mg) as yellow crystals.

5 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.34 - 1.70 (m, 4H), 2.81 (t, 2H, J = 3.6 Hz), 3.34 (t, 2H, J = 3.6 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.80 (t, 2H, J = 4.2 Hz), 4.16 (t, 2H, J = 5.6 Hz), 4.72 (s, 2H), 6.96 - 7.04 (m, 5H), 7.26 - 7.31 (m, 1H), 7.41 - 7.49 (m, 3H), 7.55 (d, 1H, J = 2.2 Hz), 7.89 (s, 1H).

Anal. Calcd. C<sub>28</sub>H<sub>31</sub>NO<sub>4</sub>S Calcd. C, 70.41; H, 6.54; N, 2.93. Found C, 70.15; H, 6.51; N, 2.79.

#### Reference Example 176

To a solution of methyl 7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 3-furaldehyde (378mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxymethylborohydride (416mg), and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give methyl 1-(3-furylmethyl)-



7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (362mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.4 Hz), 1.57 - 1.70 (m, 2H), 2.76 (t, 2H, J = 5.2 Hz), 3.27 (t, 2H, J = 5.2 Hz), 3.51 (t, 2H, J = 7.0 Hz), 3.79 - 3.84 (m, 5H), 4.16 (t, 2H, J = 5.2 Hz), 4.38 (s, 2H), 6.37 (d, 1H, J = 0.8 Hz), 6.96 - 7.00 (m, 3H), 7.38 - 7.49 (m, 5H), 7.54 (d, 1H, J = 2.2 Hz), 7.79 (s, 1H).

Reference Example 177

10 To a solution of methyl 1-(3-furymethyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (362mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room  
15 temperature for 5 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium  
20 sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was washed with hexane to give 1-(3-furymethyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (307mg) as yellow crystals.

25 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (t, 3H, J = 7.4 Hz), 1.60 -

1.70 (m, 2H), 2.80 (br, 2H), 3.30 (b, 2H), 3.52 (t, 2H,  $J = 6.6$  Hz), 3.81 (t, 2H,  $J = 4.0$  Hz), 4.17 (t, 2H,  $J = 5.0$  Hz), 4.40 (s, 2H), 6.39 (s, 1H), 6.95 - 7.01 (m, 3H), 7.39 - 7.49 (m, 5H), 7.54 (d, 1H,  $J = 2.2$  Hz), 7.89 (s, 1H).

5 Anal. Calcd.  $C_{27}H_{29}NO_5$  Calcd. C, 72.46; H, 6.53; N, 3.13. Found C, 72.13; H, 6.45; N, 3.00.

#### Reference Example 178

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 3-furaldehyde (365mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxyborohydride (402mg), and the mixture was stirred under nitrogen atmosphere at room temperature for 5 days. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate.

15 The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give methyl 7-(4-butoxyethoxyphenyl)-1-(3-furylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (310mg) as yellow oil.

20

$^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  0.93 (t, 3H,  $J = 7.4$  Hz), 1.34 - 1.50 (m, 2H), 1.56 - 1.69 (m, 2H), 2.76 (t, 2H,  $J = 7.2$  Hz), 3.28 (t, 2H,  $J = 5.6$  Hz), 3.55 (t, 2H,  $J = 6.6$  Hz), 3.78 - 3.83 (m, 5H), 4.16 (t, 2H,  $J = 5.0$  Hz), 4.38 (s, 2H), 6.38

25

(d, 1H, J = 0.8 Hz), 6.93 - 7.00 (m, 3H), 7.39 - 7.49 (m, 5H), 7.54 (d, 1H, J = 2.2 Hz), 7.79 (s, 1H).

Reference Example 179

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-(3-furylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (310mg) in a mixture of tetrahydrofuran (21ml) and methanol (21ml) was added 1N sodium hydroxide solution (7ml), and the mixture was stirred at room temperature for 3 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting solid was washed with hexane to give 7-(4-butoxyethoxyphenyl)-1-(3-furylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (312mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.31 - 1.45 (m, 2H), 1.55 - 1.70 (m, 2H), 2.79 (t, 2H, J = 4.6 Hz), 3.30 (t, 2H, J = 4.6 Hz), 3.56 (t, 2H, J = 6.6 Hz), 3.81 (t, 2H, J = 4.8 Hz), 4.16 (t, 2H, J = 5.0 Hz), 4.40 (s, 2H), 6.38 (s, 1H), 6.95 - 7.01 (m, 3H), 7.40 - 7.49 (m, 5H), 7.55 (d, 1H, J = 2.2 Hz), 7.90 (s, 1H).

Anal. Calcd. C<sub>28</sub>H<sub>31</sub>NO<sub>5</sub> · 0.2H<sub>2</sub>O Calcd. C, 72.29; H, 6.80; N, 3.01. Found C, 72.15; H, 6.95; N, 2.93.

## Reference Example 180

To a solution of methyl 7-(4-butoxyethoxyphenyl)-  
2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 2-  
ethoxybenzaldehyde (570mg) in 1,2-dichloroethane (10ml)  
5 was added sodium triacetoxymethylborohydride (402mg), and the  
mixture was stirred under nitrogen atmosphere at room  
temperature for 5 days. Then, water was added to the  
mixture, and the mixture was extracted with ethyl acetate.  
The organic layer was washed with saturated brine and  
10 dried with magnesium sulfate. The solvent was evaporated  
under reduced pressure, and the resulting residue was  
purified with silica gel column chromatography (hexane :  
ethyl acetate = 3 : 1) to give methyl 7-(4-  
butoxyethoxyphenyl)-1-(2-ethoxybenzyl)-2,3-dihydro-1-  
15 benzazepine-4-carboxylate (402mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.33 -  
1.64 (m, 7H), 2.81 (t, 2H, J = 4.4 Hz), 3.34 (t, 2H, J =  
4.4 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.78 - 3.82 (m, 5H),  
4.04 - 4.18 (m, 4H), 4.58 (s, 2H), 6.74 - 6.99 (m, 6H),  
20 7.14 (d, 1H, J = 7.8 Hz), 7.32 (dd, 1H, J = 8.4, 2.6 Hz),  
7.46 (d, 2H, J = 8.8 Hz), 7.54 (d, 1H, J = 2.2 Hz), 7.84 (s,  
1H).

## Reference Example 181

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-  
25 (2-ethoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate

10018321-121201

(402mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 4 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2-ethoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (297mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.34 - 1.47 (m, 5H), 1.50 - 1.65 (m, 2H), 2.83 (br, 2H), 3.37 (br, 2H), 3.55 (t, 2H, J = 6.6 Hz), 3.80 (t, 2H, J = 4.4 Hz), 4.10 (q, 2H, J = 5.0 Hz), 4.16 (t, 2H, J = 4.8 Hz), 4.59 (s, 2H), 6.82 (d, 1H, J = 8.8 Hz), 6.90 - 6.99 (m, 5H), 7.15 (d, 1H, J = 7.4 Hz), 7.26 - 7.37 (m, 1H), 7.46 (d, 2H, J = 8.8 Hz), 7.56 (d, 1H, J = 2.2 Hz), 7.94 (s, 1H).

Anal. Calcd. C<sub>32</sub>H<sub>37</sub>NO<sub>5</sub> Calcd. C, 74.54; H, 7.23; N, 2.72. Found C, 74.48; H, 7.17; N, 2.92.

#### Reference Example 182

To a solution of 3-hydroxybenzaldehyde (10.0g) in DMF (120ml) were added potassium carbonate (15.8g) and 1-bromopropane (12.1g), and the mixture was stirred under

nitrogen atmosphere at room temperature overnight. Then, water was added to the mixture, which was extracted with ethyl acetate and washed with 1N sodium hydroxide solution twice, with water three times and with saturated brine once. After dried with magnesium sulfate, the solvent was evaporated under reduced pressure to give 3-propoxybenzaldehyde (13.4g) as colorless liquid.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.05 (t, 3H, J = 7.4 Hz), 1.75 - 1.93 (m, 2H), 3.99 (t, 2H, J = 6.6 Hz), 7.15 - 7.21 (m, 1H), 7.39 (d, 1H, J = 2.6 Hz), 7.41 - 7.45 (m, 2H).

#### Reference Example 183

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 3-propoxybenzaldehyde (623mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxyborohydride (804mg), and the mixture was stirred under nitrogen atmosphere at room temperature for 5 days. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give methyl 7-(4-butoxyethoxyphenyl)-1-(3-propoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (412mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.89 - 1.09 (m, 6H), 1.33 - 1.45 (m, 2H), 1.55 - 1.65 (m, 2H), 1.74 - 1.85 (m, 2H), 2.78 (t, 2H, J = 5.2 Hz), 3.31 (t, 2H, J = 5.2 Hz), 3.55 (t, 2H, J = 7.0 Hz), 3.78 - 3.83 (m, 5H), 3.90 (t, 2H, J = 6.6 Hz), 4.16 (t, 2H, J = 5.4 Hz), 4.55 (s, 2H), 6.80 - 6.89 (m, 4H), 6.97 (d, 2H, J = 8.8 Hz), 7.22 - 7.49 (m, 4H), 7.54 (d, 1H, J = 2.2 Hz), 7.82 (s, 1H).

#### Reference Example 184

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-(3-propoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (412mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 4 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(3-propoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (308mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.03 (t, 3H, J = 7.2 Hz), 1.30 - 1.50 (m, 2H), 1.50 - 1.70 (m, 2H), 1.74 - 1.85 (m, 2H), 2.81 (br, 2H), 3.35 (br, 2H), 3.56 (t,

2H, J = 6.6 Hz), 3.81 (t, 2H, J = 4.4 Hz), 4.16 (t, 2H, J =  
 5.6 Hz), 4.57 (s, 2H), 6.81 - 6.91 (m, 4H), 6.98 (d, 2H, J  
 = 8.8 Hz), 7.24 - 7.35 (m, 1H), 7.38 (dd, 1H, J = 8.4, 1.4  
 Hz), 7.47 (d, 2H, J = 8.8 Hz), 7.56 (d, 1H, J = 1.4 Hz),  
 5 7.93 (s, 1H).

Anal. Calcd.  $C_{33}H_{39}NO_5$  Calcd. C, 74.83; H, 7.42; N, 2.64.  
 Found C, 74.76; H, 7.38; N, 2.74.

#### Reference Example 185

To a solution of methyl 7-(4-butoxyethoxyphenyl)-  
 10 2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 2,5-  
 dimethoxybenzaldehyde (631mg) in 1,2-dichloroethane  
 (10ml) was added sodium triacetoxymethylborohydride (8042mg),  
 and the mixture was stirred under nitrogen atmosphere at  
 room temperature for 5 days. Then, water was added to  
 15 the mixture, and the mixture was extracted with ethyl  
 acetate. The organic layer was washed with saturated  
 brine and dried with magnesium sulfate. The solvent was  
 evaporated under reduced pressure, and the resulting  
 residue was purified with silica gel column  
 20 chromatography (hexane : ethyl acetate = 3 : 1) to give  
 methyl 7-(4-butoxyethoxyphenyl)-1-(2,5-dimethoxybenzyl)-  
 2,3-dihydro-1-benzazepine-4-carboxylate (290mg) as yellow  
 oil.

$^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  0.93 (t, 3H, J = 7.4 Hz), 1.37 -  
 25 1.45 (m, 2 H), 1.55 - 1.70 (m, 2H), 3.82 (br, 2H), 3.34 (br,



2H), 3.55 (t, 2H, J = 7.0 Hz), 3.70 (s, 3H), 3.78 - 3.84 (m, 8H), 4.16 (t, 2H, J = 5.4 Hz), 4.53 (s, 2H), 6.75 - 6.83 (m, 4H), 6.97 (d, 2H, J = 8.8 Hz), 7.30 (dd, 1H, J = 8.8, 1.3 Hz), 7.46 (d, 2H, J = 8.8 Hz), 7.57 (d, 1H, J = 1.3 Hz),  
5 7.83 (s, 1H).

Reference Example 186

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-(3-propoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (290mg) in a mixture of tetrahydrofuran (21ml) and  
10 methanol (21ml) was added 1N sodium hydroxide solution (7ml), and the mixture was stirred at room temperature for 4 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl  
15 acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2,5-dimethoxybenzyl)-2,3-dihydro-  
20 1-benzazepine-4-carboxylic acid (237mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 6.8 Hz), 1.32 - 1.45 (m, 2H), 1.50 - 1.64 (m, 2H), 2.83 (br, 2H), 3.35 (br, 2H), 3.55 (t, 2H, J = 6.6 Hz), 3.71 (s, 3H), 3.80 (t, 2H, J = 5.0 Hz), 3.84 (s, 3H), 4.16 (t, 2H, J = 5.6 Hz), 4.55 (s,  
25

2H), 6.75 - 6.83 (m, 4H), 6.97 (d, 2H,  $J = 8.8$  Hz), 7.35 (dd, 1H,  $J = 8.8, 1.3$  Hz), 7.46 (d, 2H,  $J = 8.8$  Hz), 7.54 (d, 1H,  $J = 1.3$  Hz), 7.93 (s, 1H).

Anal. Calcd.  $C_{32}H_{37}NO_6 \cdot 0.1H_2O$  Calcd. C, 72.05; H, 7.03; N, 2.63. Found C, 71.83; H, 7.18; N, 2.57.

#### Example Reference 187

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 2-fluorobenzaldehyde (471mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxymethylborohydride (402mg), and the mixture was stirred under nitrogen atmosphere at room temperature for 5 days. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane:ethyl acetate=3:1) to give methyl 7-(4-butoxyethoxyphenyl)-1-(2-fluorobenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (382mg) as yellow oil.

$^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  0.93 (t, 3H,  $J = 7.0$  Hz), 1.30 - 1.45 (m, 2H), 1.54 - 1.70 (m, 2H), 2.80 (t, 2H,  $J = 4.0$  Hz), 3.31 (t, 2H,  $J = 5.2$  Hz), 3.55 (t, 2H,  $J = 6.6$  Hz), 3.78 - 3.83 (m, 5H), 4.16 (t, 2H,  $J = 5.2$  Hz), 4.63 (s, 2H), 6.82 (d, 1H,  $J = 8.8$  Hz), 6.95 - 7.48 (m, 9H), 7.56 (d, 1H,  $J =$

2.2 Hz), 7.82 (s, 1H).

Reference Example 188

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-(2-fluorobenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (382mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 4 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to make acidic (pH = 4), and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2-fluorobenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (309mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 - 1.45 (m, 2H), 1.54 - 1.65 (m, 2H), 2.81 (br, 2H), 3.37 (br, 2H), 3.55 (t, 2H, J = 6.8 Hz), 3.80 (t, 2H, J = 4.4 Hz), 4.16 (t, 2H, J = 5.6 Hz), 4.65 (s, 2H), 6.84 (d, 1H, J = 8.4 Hz), 6.98 (d, 2H, J = 8.8 Hz), 7.06 - 7.15 (m, 2H), 7.24 - 7.40 (m, 3H), 7.46 (d, 2H, J = 8.8 Hz), 7.57 (d, 1H, J = 2.6 Hz), 7.93 (s, 1H).

Anal. Calcd. C<sub>30</sub>H<sub>32</sub>NO<sub>4</sub>F Calcd. C, 73.60; H, 6.59; N, 2.86. Found C, 73.48; H, 6.46; N, 3.01.

## Reference Example 189

To a solution of methyl 7-(4-butoxyethoxyphenyl)-  
2,3-dihydro-1-benzazepine-4-carboxylate (500mg) and 1-  
methyl-2-imidazolecarboxyaldehyde (696mg) in 1,2-  
5 dichloroethane (20ml) was added sodium  
triacetoxymethylborohydride (804mg), and the mixture was  
stirred under nitrogen atmosphere at room temperature for  
4 days. Then, water was added to the mixture, and the  
mixture was extracted with ethyl acetate. The organic  
10 layer was washed with saturated brine and dried with  
magnesium sulfate. The solvent was evaporated under  
reduced pressure, and the resulting residue was purified  
with silica gel column chromatography (ethyl acetate) to  
give methyl 7-(4-butoxyethoxyphenyl)-1-[(1-  
15 methylimidazol-2-yl)methyl]-2,3-dihydro-1-benzazepine-4-  
carboxylate (367mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.38 -  
1.45 (m, 2H), 1.54 - 1.65 (m, 2H), 2.41 (t, 2H, J = 4.4 Hz),  
3.30 (t, 2H, J = 5.0 Hz), 3.51 (s, 3H), 3.56 (t, 2H, J =  
20 6.2 Hz), 3.79 - 3.83 (m, 5H), 4.17 (t, 2H, J = 4.4 Hz),  
4.61 (s, 2H), 6.88 (d, 1H, J = 1.0 Hz), 6.97 - 7.06 (m, 4H),  
7.44 - 7.50 (m, 3H), 7.56 (d, 2H, J = 2.2 Hz), 7.77 (s, 1H).

## Reference Example 190

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-  
25 [(1-methylimidazol-2-yl)methyl]-2,3-dihydro-1-

benzazepine-4-carboxylate (367mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 3 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to neutralize, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(1-methylimidazol-2-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (285mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.30 - 1.50 (m, 2H), 1.54 - 1.70 (m, 2H), 2.47 (br, 2H), 3.32 (br, 2H), 3.54 - 3.59 (m, 5H), 3.80 (t, 2H, J = 4.4 Hz), 4.16 (t, 2H, J = 5.4 Hz), 4.68 (s, 2H), 6.88 (s, 1H), 6.98 (d, 2H, J = 8.4 Hz), 7.03 - 7.07 (m, 2H), 7.45 - 7.49 (m, 3H), 7.57 (d, 1H, J = 2.2 Hz), 7.85 (s, 1H).

Anal. Calcd. C<sub>28</sub>H<sub>35</sub>N<sub>3</sub>O<sub>4</sub> Calcd. C, 70.42; H, 7.39; N, 8.80. Found C, 70.27; H, 7.43; N, 8.73.

#### Reference Example 191

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 2-thiazolecarboxyaldehyde (445mg) in 1,2-dichloroethane

(20ml) was added sodium triacetoxyborohydride (416mg), and the mixture was stirred under nitrogen atmosphere at room temperature for 1 day. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate.

5 The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give methyl 7-(4-  
10 butoxyethoxyphenyl)-1-(thiazol-2-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (212mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 - 1.45 (m, 2H), 1.57 - 1.70 (m, 2H), 2.87 (t, 2H, J = 4.4 Hz), 3.42 (t, 2H, J = 4.4 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.78 -  
15 3.82 (m, 5H), 4.16 (t, 2H, J = 5.6 Hz), 4.86 (s, 2H), 6.95 - 7.00 (m, 3H), 7.30 (d, 1H, J = 3.2 Hz), 7.40 (dd, 1H, J = 8.4, 2.2 Hz), 7.46 (d, 2H, J = 8.6 Hz), 7.56 (d, 1H, J = 2.6 Hz), 7.78 - 7.81 (m, 2H).

#### Reference Example 192

20 To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-(thiazol-2-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (212mg) in a mixture of tetrahydrofuran (18ml) and methanol (18ml) was added 1N sodium hydroxide solution (6ml), and the mixture was stirred at room  
25 temperature overnight. Then, to the mixture was added

water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(thiazol-2-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (153mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.6 Hz), 1.34 - 1.45 (m, 2H), 1.54 - 1.65 (m, 2H), 2.89 (br, 2H), 3.45 (br, 2H), 3.55 (t, 2H, J = 6.6 Hz), 3.80 (t, 2H, J = 4.4 Hz), 4.16 (t, 2H, J = 5.6 Hz), 4.88 (s, 2H), 6.96 - 7.01 (m, 3H), 7.31 (d, 1H, J = 3.2 Hz), 7.46 - 7.49 (m, 3H), 7.57 (d, 1H, J = 2.6 Hz), 7.80 (d, 1H, J = 3.4 Hz), 7.91 (s, 1H).

Anal. Calcd. C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>S Calcd. C, 67.76; H, 6.32; N, 5.85. Found C, 67.76; H, 6.39; N, 5.70.

#### Reference Example 193

To a solution of methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (1.5g) and 2-methoxybenzaldehyde (3.62g) in 1,2-dichloroethane (50ml) was added sodium triacetoxymethylborohydride (2.82g), and the mixture was stirred under nitrogen atmosphere at room temperature for 1 day. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate.

The organic layer was washed with saturated brine and

dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane:ethyl acetate=5:1) to give methyl 7-bromo-1-(2-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (1.62g) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.79 (t, 2H, J = 5.2 Hz), 3.29 (t, 2H, J = 5.6 Hz), 3.80 (s, 3H), 3.86 (s, 3H), 4.50 (s, 2H), 6.60 (d, 1H, J = 9.2 Hz), 6.88 - 7.07 (m, 3H), 7.16 (dd, 1H, J = 8.8, 2.6 Hz), 7.20 - 7.31 (m, 1H), 7.46 (d, 1H, J = 2.6 Hz), 7.64 (s, 1H).

#### Reference Example 194

In toluene (25ml), ethanol (2.5ml) and water (2.5ml) were suspended methyl 7-bromo-1-(2-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (712mg), 4-propoxyphenyl borate (416mg) and potassium carbonate (636mg), and the suspension was stirred under argon atmosphere for 30 minutes. Then, to the suspension was added tetrakis(triphenylphosphine)palladium (143mg) and the mixture was heated under argon atmosphere at 100°C for 5 hours. After allowing to cool, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified



with silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give methyl 7-(4-propoxyphenyl)-1-(2-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (663mg) as yellow oil.

5 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.05 (t, 3H, J = 7.2 Hz), 1.81 - 1.88 (m, 2H), 2.82 (t, 2H, J = 5.2 Hz), 3.34 (t, 2H, J = 5.2 Hz), 3.82 (s, 3H), 3.88 (s, 3H), 3.95 (t, 2H, J = 6.6 Hz), 4.56 (s, 2H), 6.76 - 7.15 (m, 6H), 7.26 - 7.35 (m, 2H), 7.45 (d, 2H, J = 8.8 Hz), 7.57 - 7.60 (m, 1H), 7.84 (s, 1H).

10 Reference Example 195

To a solution of methyl 7-(propoxyphenyl)-1-(2-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (601mg) in a mixture of tetrahydrofuran (39ml) and methanol (39ml) was added 1N sodium hydroxide solution (13ml), and the mixture was stirred at room temperature for 4 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-propoxyphenyl)-1-(2-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (406mg) as yellow crystals.

25 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.05 (t, 3H, J = 7.2 Hz), 1.77 -

1.88 (m, 2H), 2.84 (t, 2H, J = 4.8 Hz), 3.37 (t, 2H, J = 4.8 Hz), 3.88 (s, 3H), 3.95 (t, 2H, J = 6.6 Hz), 4.58 (s, 2H), 6.79 d, 1H, J = 8.8 Hz), 6.92 - 6.96 (m, 4H), 7.14 (d, 1H, J = 6.0 Hz), 7.26 - 7.37 (m, 2H), 7.46 (d, 2H, J = 8.8 Hz), 7.56 (d, 1H, J = 2.2 Hz), 7.95 (s, 1H).

Anal. Calcd.  $C_{29}H_{29}NO_4 \cdot 0.3H_2O$  Calcd. C, 75.56; H, 6.47; N, 3.04. Found C, 75.47; H, 6.58; N, 3.04.

#### Reference Example 196

To a suspension of 60% sodium hydride (1.5g) in dry tetrahydrofuran (30ml) which had been washed with hexane three times was added dropwise a solution of 4-bromopyrazole (5.0g) in dry tetrahydrofuran (30ml) under nitrogen atmosphere at 0°C, the temperature was returned to room temperature, and the mixture was stirred for 1 hour. To the mixture was added dropwise a solution of methyl iodide (5.31g) in dry tetrahydrofuran (20ml) under nitrogen atmosphere at 0°C, the temperature was returned to room temperature, and the mixture was stirred for 3 hours. The solution was diluted with tetrahydrofuran, and the insolubles were filtered with Celite. After the filtrate was concentrated under reduced pressure, hexane was further added, and the insolubles were filtered. The filtrate was concentrated under reduced pressure to give 4-bromo-1-methylpyrazole (5.12g) as light yellow liquid.

$^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  3.89 (s, 3H), 7.38 (s, 1H), 7.44

(s, 1H).

Reference Example 197

To a solution of 4-bromo-1-methylpyrazole (3.0g) in dry tetrahydrofuran (50ml) was added dropwise n-  
5 butyllithium (14.0ml, 1.6M solution in hexane) under nitrogen atmosphere at -78°C. After 30 minutes, DMF (6.8g) was added dropwise under nitrogen atmosphere at -78°C, the temperature was returned to room temperature, and the mixture was stirred for 1 hour. Then, 1N  
10 hydrochloric acid (50ml) was added thereto at 0°C, and the mixture was stirred for 30 minutes, made basic with 1N sodium hydroxide solution and extracted with ethyl acetate three times. The extract was dried with magnesium sulfate, the solvent was evaporated under  
15 reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 1 : 2) to give 1-methylpyrazole-4-carboxyaldehyde (540mg) as light yellow oil.  
<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 3.97 (s, 3H), 7.91 (s, 1H), 7.96  
20 (s, 1H), 9.86 (s, 1H).

Reference Example 198

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (388mg) and 1-methylpyrazole-4-carboxyaldehyde (540mg) in 1,2-  
25 dichloroethane (15ml) was added sodium

10018321.121201  
triacetoxymethylborohydride (519mg), and the mixture was stirred under nitrogen atmosphere at room temperature for 1 day. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 2 : 3) to give methyl 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylate (321mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.34 - 1.45 (m, 2H), 1.50 - 1.70 (m, 2H), 2.76 (t, 2H, J = 5.0 Hz), 3.27 (t, 2H, J = 5.0 Hz), 3.56 (t, 2H, J = 7.0 Hz), 3.78 - 3.83 (m, 5H), 3.89 (s, 3H), 4.16 (t, 2H, J = 5.2 Hz), 4.42 (s, 2H), 6.92 - 7.00 (m, 3H), 7.29 (s, 1H), 7.40 (dd, 1H, J = 8.4, 1.8 Hz), 7.45 - 7.49 (m, 3H), 7.54 (d, 1H, J = 2.2 Hz), 7.78 (s, 1H).

#### Reference Example 199

20 To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylate (321mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 3 days. Then, to the mixture was added

Ammon.  
B48

water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (239mg) as yellow crystals.

10 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.34 - 1.49 (m, 2H), 1.55 - 1.65 (m, 2H), 2.79 (t, 2H, J = 4.2 Hz), 3.30 (t, 2H, J = 4.2 Hz), 3.56 (t, 2H, J = 8.6 Hz), 3.81 (t, 2H, J = 4.8 Hz), 3.90 (s, 3H), 4.16 (t, 2H, J = 5.2 Hz), 4.44 (s, 2H), 6.94 - 7.01 (m, 3H), 7.30 (s, 1H), 7.40 - 7.50 (m, 4H), 7.56 (d, 1H, J = 2.0 Hz), 7.90 (s, 1H).

Anal. Calcd. C<sub>28</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub>, Calcd. C, 70.71; H, 6.99; N, 8.84. Found C, 70.52; H, 6.90; N, 8.70.

#### Reference Example 200

To a solution of 1-methylpyrazole (10.0g) in dry tetrahydrofuran (200ml) was added dropwise n-butyllithium (91.3ml, 1.6M solution in hexane) at -78°C under nitrogen atmosphere. After 30 minutes, DMF (44.6g) was added dropwise thereto at -78°C under nitrogen atmosphere, the temperature was returned to room temperature, and the mixture was stirred for 2 hours. Then, to the mixture

was added 1N hydrochloric acid (200ml) at 0°C, the mixture was stirred for 30 minutes, made basic with 1N sodium hydroxide solution, and extracted with ethyl acetate three times. The mixture was dried with magnesium sulfate, and the solvent was evaporated under reduced pressure to give 1-methyl-5-pyrazolecarboxyaldehyde (11.7g) as light yellow oil. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 4.19 (s, 3H), 6.90 (d, 1H, J = 2.2 Hz), 7.54 (d, 1H, J = 1.8 Hz), 9.88 (s, 1H).

10 Reference Example 201

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (500mg) and 1-methylpyrazole-5-carboxyaldehyde (696mg) in 1,2-dichloroethane (15ml) was added sodium triacetoxymethylborohydride (670mg), and the mixture was stirred under nitrogen atmosphere at room temperature for 1 day. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 2 : 3) to give methyl 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylate (391mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.34 - 1.45 (m, 2H), 1.55 - 1.70 (m, 2H), 2.58 (t, 2H, J = 4.8 Hz), 3.27 (t, 2H, J = 4.8 Hz), 3.56 (t, 2H, J = 7.0 Hz), 3.79 - 3.83 (m, 8H), 4.17 (t, 2H, J = 4.4 Hz), 4.52 (s, 2H), 6.22 (d, 1H, J = 1.8 Hz), 6.92 (d, 1H, J = 8.8 Hz), 6.99 (d, 2H, J = 8.8 Hz), 7.40 - 7.50 (m, 4H), 7.57 (d, 1H, J = 2.2 Hz), 7.79 (s, 1H).

## Reference Example 202

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-  
10 [(1-methylpyrazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylate (391mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 3 days. Then, to the mixture was added  
15 water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was  
20 recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(1-methylpyrazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (263mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.34 - 1.45 (m, 2H), 1.55 - 1.65 (m, 2H), 2.62 (br, 2H), 3.30 (br,

2H), 3.56 (t, 2H, J = 7.0 Hz), 3.79 - 3.84 (m, 5H), 4.17 (t, 2H, J = 5.0 Hz), 4.54 (s, 2H), 6.22 (d, 1H, J = 1.8 Hz), 6.93 (d, 1H, J = 8.8 Hz), 6.99 (d, 2H, J = 8.8 Hz), 7.43 - 7.50 (m, 4H), 7.58 (d, 1H, J = 2.2 Hz), 7.89 (s, 1H).

5 Anal. Calcd.  $C_{28}H_{33}N_3O_4$ , Calcd. C, 70.71; H, 6.99; N, 8.84. Found C, 70.48; H, 6.90; N, 8.80.

#### Reference Example 203

2,5-dimethylisooxazole (10.0g) was dissolved in water (100ml). To the solution were added concentrated  
10 sulfuric acid (35.3g) and 40% aqueous formaldehyde solution (46.4g) at 0°C, and the mixture was heated at 70°C overnight. The mixture was neutralized with 1N sodium hydroxide solution at 0°C and extracted with chloroform three times. The extract was dried with  
15 magnesium sulfate, the solvent was evaporated under reduced pressure, and the resulting residue was distilled under reduced pressure to give 4-hydroxymethyl-2,5-dimethylisooxazole (2.54g) as colorless liquid.  
 $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.31 (s, 3H), 2.39 (s, 3H), 4.48  
20 (s, 2H).

#### Reference Example 204

To a solution of 4-hydroxymethyl-2,5-dimethylisooxazole (2.45g) in ethyl acetate (500ml) was added active manganese dioxide (24.5g), and the mixture  
25 was stirred at room temperature for 3 days. The

10018321-121201  
FOI217-12287007



insolubles were filtered using Celite, and the filtrate was concentrated under reduced pressure to give 2,3-dimethylisooxazole-4-carboxyaldehyde (1.5g) as colorless oil.

5  $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.42 (s, 3H), 2.69 (s, 3H), 9.95 (s, 1H).

Reference Example 205

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (500mg) and 2,5-dimethylisooxazole-4-carboxyaldehyde (791mg) in 1,2-dichloroethane (15ml) was added sodium triacetoxymethylborohydride (2.0g), and the mixture was stirred under nitrogen atmosphere at room temperature for 7 days. Then, water was added to the mixture, and the mixture was  
15 extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate  
20 = 3 : 1) to give methyl 7-(4-butoxyethoxyphenyl)-1-[(2,5-diethylisooxazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylate (309mg) as yellow oil.

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.94 (t, 3H,  $J = 7.4$  Hz), 1.34 - 1.48 (m, 2H), 1.49 - 1.68 (m, 2H), 2.19 (s, 3H), 2.27 (s, 3H), 2.59 (t, 2H,  $J = 4.0$  Hz), 3.13 (t, 2H,  $J = 4.4$  Hz),  
25

3.56 (t, 2H, J = 6.6 Hz), 3.79 - 3.84 (m, 5H), 4.17 (t, 2H, J = 4.6 Hz), 4.26 (s, 2H), 6.93 (d, 1H, J = 8.4 Hz), 6.99 (d, 2H, J = 8.8 Hz), 7.42 - 7.50 (m, 3H), 7.57 (d, 1H, J = 2.2 Hz), 7.78 (s, 1H).

5           Reference Example 206

10           To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-  
            [(1-methylpyrazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-  
            4-carboxylate (222mg) in a mixture of tetrahydrofuran  
            (13ml) and methanol (13ml) was added 1N sodium hydroxide  
            solution (4.4ml), and the mixture was stirred at room  
            temperature for 4 days. Then, to the mixture was added  
            water at 0°C, and 1N hydrochloric acid was further added  
            to neutral, and the mixture was extracted with ethyl  
            acetate. The organic layer was washed with water and  
15           saturated brine and dried with magnesium sulfate. The  
            solvent was evaporated under reduced pressure, which was  
            recrystallized from hexane-ethyl acetate to give 7-(4-  
            butoxyethoxyphenyl)-1-[(2,5-dimethylisoxazol-4-  
            yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid  
20           (164mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.0 Hz), 1.34 -  
            1.45 (m, 2H), 1.55 - 1.65 (m, 2H), 2.20 (s, 3H), 2.39 (s,  
            3H), 2.62 (br, 2H), 3.16 (br, 2H), 3.56 (t, 2H, J = 6.6 Hz),  
            3.81 (t, 2H, J = 4.4 Hz), 4.17 (t, 2H, J = 5.0 Hz), 4.28 (s,  
25           2H), 6.93 - 7.02 (m, 3H), 7.46 - 7.51 (m, 3H), 7.58 (d, 1H,

10018321-121201

$J = 2.2 \text{ Hz}$ ), 7.87 (s, 1H).

Anal. Calcd.  $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_5$ , Calcd. C, 70.85; H, 7.18; N, 5.70.

Found C, 70.71; H, 6.90; N, 5.43.

#### Reference Example 207

- 5 To a solution of methyl 7-(4-butoxyethoxyphenyl)-  
2,3-dihydro-1-benzazepine-4-carboxylate (400mg) and  
furfural (485mg) in 1,2-dichloroethane (15ml) was added  
sodium triacetoxymethylborohydride (536mg), and the mixture was  
stirred under nitrogen atmosphere at room temperature for  
10 1 day. Then, water was added to the mixture, and the  
mixture was extracted with ethyl acetate. The organic  
layer was washed with saturated brine and dried with  
magnesium sulfate. The solvent was evaporated under  
reduced pressure, and the resulting residue was purified  
15 with silica gel column chromatography (hexane : ethyl  
acetate = 3 : 1) to give methyl 7-(4-butoxyethoxyphenyl)-  
1-(2-furylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate  
(319mg) as yellow oil.
- $^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (t, 3H,  $J = 7.4 \text{ Hz}$ ), 1.30 -  
20 1.45 (m, 2H), 1.46 - 1.70 (m, 2H), 2.77 (t, 2H,  $J = 4.0 \text{ Hz}$ ),  
3.30 (t, 2H,  $J = 4.4 \text{ Hz}$ ), 3.55 (t, 2H,  $J = 6.6 \text{ Hz}$ ), 3.78 -  
3.83 (m, 5H), 4.16 (t, 2H,  $J = 5.0 \text{ Hz}$ ), 4.49 (s, 2H), 6.28  
(d, 2H,  $J = 3.4 \text{ Hz}$ ), 6.37 (dd, 1H,  $J = 2.8, 1.8 \text{ Hz}$ ), 6.98  
(d, 2H,  $J = 8.8 \text{ Hz}$ ), 7.06 (d, 1H,  $J = 8.8 \text{ Hz}$ ), 7.41 - 7.50  
25 (m, 4H), 7.54 (d, 1H,  $J = 2.2 \text{ Hz}$ ), 7.79 (s, 1H).

## Reference Example 208

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-(2-furylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (319mg) in a mixture of tetrahydrofuran (21ml) and methanol (21ml) was added 1N sodium hydroxide solution (7ml), and the mixture was stirred at room temperature for 5 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2-furylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (256mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.34 - 1.50 (m, 2H), 1.55 - 1.70 (m, 2H), 2.79 (t, 2H, J = 4.4 Hz), 3.33 (t, 2H, J = 4.4 Hz), 3.56 (t, 2H, J = 6.6 Hz), 3.81 (t, 2H, J = 4.8 Hz), 4.17 (t, 2H, J = 4.8 Hz), 4.50 (s, 2H), 6.29 (d, 1H, J = 3.2 Hz), 6.38 (dd, 1H, J = 2.8, 1.8 Hz), 6.99 (d, 2H, J = 8.8 Hz), 7.08 (d, 1H, J = 9.0 Hz), 7.42 - 7.50 (m, 4H), 7.55 (d, 1H, J = 2.2 Hz), 7.90 (s, 1H).

Anal. Calcd. C<sub>28</sub>H<sub>31</sub>NO<sub>5</sub> Calcd. C, 72.86; H, 6.77; N, 3.03. Found C, 72.63; H, 6.67; N, 2.82.

## 25 Reference Example 209

To a solution of methyl 7-(4-butoxyethoxyphenyl)-  
2,3-dihydro-1-benzazepine-4-carboxylate (400mg) and  
pyridine-2-carboxyaldehyde (542mg) in 1,2-dichloroethane  
(15ml) was added sodium triacetoxyborohydride (1.07g),  
5 and the mixture was stirred under nitrogen atmosphere at  
room temperature for 4 days. Then, water was added to  
the mixture, and the mixture was extracted with ethyl  
acetate. The organic layer was washed with saturated  
brine and dried with magnesium sulfate. The solvent was  
10 evaporated under reduced pressure, and the resulting  
residue was purified with silica gel column  
chromatography (hexane : ethyl acetate = 1 : 1) to give  
methyl 7-(4-butoxyethoxyphenyl)-1-(2-pyridylmethyl)-2,3-  
dihydro-1-benzazepine-4-carboxylate (378mg) as yellow oil.  
15 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 -  
1.45 (m, 2H), 1.50 - 1.65 (m, 2H), 2.84 (t, 2H, J = 4.4 Hz),  
3.40 (t, 2H, J = 4.4 Hz), 3.55 (t, 2H, J = 6.8 Hz), 3.78 -  
3.82 (m, 5H), 4.15 (t, 2H, J = 5.2 Hz), 4.71 (s, 2H), 6.82  
(d, 1H, J = 8.8 Hz), 6.97 (d, 2H, J = 8.8 Hz), 7.21 - 7.29  
20 (m, 2H), 7.35 (dd, 1H, J = 8.8, 2.2 Hz), 7.46 (d, 2H, J =  
8.8 Hz), 7.56 (d, 1H, J = 2.2 Hz), 7.67 (td, 1H, J = 9.0,  
2.0 Hz), 7.83 (s, 1H), 8.62 (d, 1H, J = 4.0 Hz).

## Reference Example 210

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-  
25 (2-pyridylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate

(378mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 2 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2-pyridylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (260mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.30 - 1.48 (m, 2H), 1.54 - 1.68 (m, 2H), 2.87 (t, 2H, J = 4.4 Hz), 3.43 (t, 2H, J = 4.4 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.80 (t, 2H, J = 5.6 Hz), 4.74 (s, 2H), 6.83 (d, 1H, J = 8.8 Hz), 6.97 (d, 2H, J = 8.8 Hz), 7.20 - 7.31 (m, 2H), 7.37 (dd, 1H, J = 8.8, 2.2 Hz), 7.46 (d, 2H, J = 8.4 Hz), 7.58 (d, 1H, J = 1.8 Hz), 7.69 (td, 1H, J = 7.8, 2.0 Hz), 7.94 (s, 1H), 8.64 (d, 1H, J = 5.2 Hz).

Anal. Calcd. C<sub>29</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub> · 0.3H<sub>2</sub>O Calcd. C, 72.87; H, 6.87; N, 5.86. Found C, 72.74; H, 6.73; N, 5.69.

#### Reference Example 211

To a solution of acetamide (4.0g) in tetrahydrofuran (300ml) was added sodium hydrogen carbonate (28.4g),

10018321-121201  
followed by addition of 80% ethyl bromopyruvate (21.5g)  
at 0°C. The mixture was heated at 85°C overnight, the  
temperature was returned to room temperature, the  
insolubles were filtered using Celite and the solvent was  
5 evaporated under reduced pressure. The resulting residue  
was dissolved in tetrahydrofuran (150ml), and to the  
solution was added dropwise trifluoroacetic anhydride at  
0°C. After concentrated under reduced pressure, to the  
mixture was added ethyl acetate, and the mixture was  
10 washed with saturated sodium hydrogen carbonate solution  
twice and further with saturated brine and dried with  
magnesium sulfate. The solvent was evaporated under  
reduced pressure, followed by distillation under reduced  
pressure to give ethyl 2-methyloxazole-4-carboxylate  
15 (4.67g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.38 (t, 3H, J = 7.4 Hz), 2.54 (s,  
3H), 4.39 (q, 2H, J = 7.4 Hz), 8.14 (s, 1H).

#### Reference Example 212

A suspension of aluminum lithium hydride (553mg) in  
20 tetrahydrofuran (20ml) was added dropwise a solution of  
ethyl 2-methyl-oxazole-4-carboxylate (2.26g) in  
tetrahydrofuran (20ml) under nitrogen atmosphere, and the  
mixture was stirred at room temperature for 6 hours. To  
the mixture were successively added water (0.55ml), 15%  
25 sodium hydroxide solution (0.55ml) and water (1.65ml),

the mixture was stirred at room temperature for 2 hours and dried with magnesium sulfate. The insolubles were filtered using Celite, and the solvent was evaporated under reduced pressure to give 4-hydroxymethyl-2-methyloxazole (1.11g).

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.45 (s, 3H), 4.56 (d, 2H,  $J = 1.0$  Hz), 7.48 (s, 1H).

#### Reference Example 213

To a solution of oxalyl chloride (3.53g) in dichloromethane (100ml) was added dropwise a solution of DMSO (2.89g) in dichloromethane (10ml) at  $-78^\circ\text{C}$ . Then, to the mixture was added dropwise a solution of 4-hydroxymethyl-2-methyloxazole in dichloromethane (50ml), and the mixture was stirred at  $-45^\circ\text{C}$  for 1 hour. Then, to the mixture was added dropwise triethylamine (10.3g) at  $-45^\circ\text{C}$ , and the mixture was stirred at  $0^\circ\text{C}$  for 30 minutes. To the mixture were added saturated aqueous ammonium chloride solution (50ml) and water (200ml), and the mixture was extracted with ethyl acetate and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane:ethyl acetate=1:1) to give 2-methyloxazole-4-carboxyaldehyde (0.10g) as brown crystals.

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.55 (s, 3H), 8.17 (s, 1H), 9.91



(s, 1H).

Reference Example 214

To a solution of thioacetamide (11.9g) in tetrahydrofuran (600ml) was added sodium hydrogen carbonate (66.4g), followed by addition of 80% ethyl bromopyruvate (50.0g) at 0°C. The mixture was stirred overnight, the insolubles were filtered using Celite and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in tetrahydrofuran (170ml), and to the solution was added dropwise trifluoroacetic anhydride (170ml) at 0°C, and the mixture was stirred at room temperature for 1 hour. To the mixture was added dropwise pyridine (200ml) at 0°C, and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure, to the mixture was added ethyl acetate, and the mixture was washed with saturated sodium hydrogen carbonate solution and further with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give ethyl 2-methylthiazole-4-carboxylate (13.0g) as brown crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.41 (t, 3H, J = 7.4 Hz), 2.78 (s, 3H), 4.43 (q, 2H, J = 7.4 Hz), 8.04 (s, 1H).

## Reference Example 215

100183EEL-121201  
A suspension of aluminum lithium hydride (0.89g) in tetrahydrofuran (20ml) was added dropwise a solution of ethyl 2-methylthiazole-4-carboxylate (4.00g) in  
5 tetrahydrofuran (30ml) under nitrogen atmosphere, and the mixture was stirred at room temperature for 2 hours. To the mixture were successively added water (0.9ml), 15% sodium hydroxide solution (0.9ml) and water (2.7ml), the mixture was stirred at room temperature for 2 hours and  
10 dried with magnesium sulfate. The insolubles were filtered using Celite, and the solvent was evaporated under reduced pressure to give 4-hydroxymethyl-2-methylthiazole (2.18g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.71 (s, 3H), 4.73 (d, 2H, J = 0.8  
15 Hz), 7.03 (s, 1H).

## Reference Example 216

To a solution of 4-hydroxymethyl-2-methylthiazole (2.18g) in ethyl acetate (50ml) was added active manganese (21.8g), and the mixture was stirred at room  
20 temperature for 1 day. The insolubles were filtered using Celite, and the filtrate was concentrated under reduced pressure to give 2-methylthiazole-4-carboxyaldehyde (0.9g) as brown oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.80 (s, 3H), 8.05 (s, 1H), 9.99  
25 (s, 1H).

## Reference Example 217

To a solution of methyl 7-(4-butoxyethoxyphenyl)-  
2,3-dihydro-1-benzazepine-4-carboxylate (500mg) and 2-  
methylthiazole-4-carboxyaldehyde (804mg) in 1,2-  
5 dichloroethane (20ml) was added sodium  
triacetoxymethylborohydride (1.6g), and the mixture was stirred  
under nitrogen atmosphere at room temperature for 4 days.  
Then, water was added to the mixture, and the mixture was  
extracted with ethyl acetate. The organic layer was  
10 washed with saturated brine and dried with magnesium  
sulfate. The solvent was evaporated under reduced  
pressure, and the resulting residue was purified with  
silica gel column chromatography (hexane : ethyl acetate  
= 3 : 2) to give methyl 7-(4-butoxyethoxyphenyl)-1-[(2-  
15 methylthiazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-  
carboxylate (550mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.34 -  
1.45 (m, 2H), 1.54 - 1.65 (m, 2H), 2.74 (s, 3H), 2.83 (t,  
2H, J = 4.4 Hz), 3.38 (t, 2H, J = 4.0 Hz), 3.55 (t, 2H, J =  
20 6.6 Hz), 3.78 - 3.83 (m, 5H), 4.16 (t, 2H, J = 5.0 Hz),  
4.65 (s, 2H), 6.89 - 6.99 (m, 4H), 7.37 (dd, 1H, J = 8.8,  
2.2 Hz), 7.46 (d, 2H, J = 8.8 Hz), 7.54 (d, 1H, J = 2.2 Hz),  
7.81 (s, 1H).

## Reference Example 218

25 To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-

[(2-methylthiazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylate (550mg) in a mixture of tetrahydrofuran (33ml) and methanol (33ml) was added solution (11ml), and the mixture was stirred at room temperature for 2 days.

5 Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under  
10 reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(2-methylthiazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (427mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 -  
15 1.45 (m, 2H), 1.58 - 1.65 (m, 2H), 2.75 (s, 3H), 2.85 (t, 2H, J = 4.4 Hz), 3.40 (t, 2H, J = 4.4 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.80 (t, 2H, J = 4.4 Hz), 4.16 (t, 2H, J = 5.4 Hz), 4.66 (s, 2H), 6.90 - 7.00 (m, 4H), 7.40 (dd, 1H, J = 9.4, 2.6 Hz), 7.46 (d, 2H, J = 8.8 Hz), 7.55 (d, 1H, J = 2.2 Hz),  
20 7.91 (s, 1H).

Anal. Calcd. C<sub>28</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub> Calcd. C, 68.27; H, 6.55; N, 5.69.  
Found C, 68.25; H, 6.69; N, 5.82.

#### Reference Example 219

In water (28ml) and ice (100cc) was suspended 5-  
25 amino-3-methylisothiazole hydrochloride (10.0g), and

10018321-124201

concentrated sulfuric acid (28ml) was added to the suspension. Then, to the mixture was added dropwise a solution of sodium nitrite (4.82g) in water (100ml) at 0°C. The mixture was stirred at 0°C for 1 hour, and a solution of potassium iodide (11.6g) in water (70ml) was added dropwise to the mixture at 0°C. Then, the mixture was heated at 80°C for 1 hour, and to the mixture was added ethyl acetate at 0°C, and the mixture was neutralized with potassium carbonate. After separation, the organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and origin components were removed by silica gel column chromatography (ethyl acetate) to give 5-iodo-3-methylisothiazole (10.6g) as deep brown oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.51 (s, 3H), 7.15 (s, 1H).

#### Reference Example 220

To a solution of 5-iodo-3-methylisothiazole (10.0g) in dry tetrahydrofuran (150ml) was added dropwise n-butyllithium (33.3ml, 1.6M solution in hexane) at -78°C under nitrogen atmosphere. After 30 minutes, to the mixture was added dropwise DMF (9.7g) at -78°C under nitrogen atmosphere, the temperature was returned to room temperature, and the mixture was stirred for 2 hours. Then, to the mixture was added 1N hydrochloric acid

(75ml) at 0°C, and the mixture was stirred for 30 minutes and extracted with ethyl acetate. The extract was dried with magnesium sulfate, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (ethyl acetate) to remove origin components to give 3-methylisothiazole-5-carboxyaldehyde (5.0g) as deep brown oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.59 (s, 3H), 7.54 (s, 1H), 10.08 (s, 1H).

10           Reference Example 221

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (500mg) and 3-methylthiazole-5-carboxyaldehyde(803mg) in 1,2-dichloroethane (15ml) was added sodium triacetoxymethylborohydride (807mg), and the mixture was stirred under nitrogen atmosphere at room temperature for 1 day. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1) to give methyl 7-(4-butoxyethoxyphenyl)-1-[(3-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-5-carboxylate (640mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 - 1.45 (m, 2H), 1.50 - 1.70 (m, 2H), 2.48 (s, 3H), 2.85 (t, 2H, J = 4.4 Hz), 3.34 (t, 2H, J = 4.8 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.78 - 3.82 (m, 5H), 4.16 (t, 2H, J = 5.0 Hz), 4.76 (s, 2H), 6.87 - 7.00 (m, 4H), 7.41 (dd, 1H, J = 8.8, 2.2 Hz), 7.47 (d, 2H, J = 8.8 Hz), 7.56 (d, 1H, J = 2.2 Hz), 7.80 (s, 1H).

#### Reference Example 222

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-[(3-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylate (640mg) in a mixture of tetrahydrofuran (39ml) and methanol (39ml) was added 1N sodium hydroxide solution (13ml), and the mixture was stirred at room temperature for 1 day. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(3-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (460mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 - 1.45 (m, 2H), 1.55 - 1.69 (m, 2H), 2.49 (s, 3H), 2.87 (t,

2H,  $J = 4.4$  Hz), 3.37 (t, 2H,  $J = 4.4$  Hz), 3.56 (t, 2H,  $J = 6.6$  Hz), 3.81 (t, 2H,  $J = 4.4$  Hz), 4.16 (t, 2H,  $J = 5.0$  Hz), 4.78 (s, 2H), 6.89 - 7.01 (m, 4H), 7.40 - 7.49 (m, 3H), 7.58 (d, 1H,  $J = 1.8$  Hz), 7.91 (s, 1H).

5 Anal. Calcd.  $C_{28}H_{32}N_2O_4S$  Calcd. C, 68.27; H, 6.55; N, 5.69. Found C, 67.94; H, 6.55; N, 5.97.

Reference Example 223

*Amen. B49*

To a solution of methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (200mg) and pyridine (123mg) in tetrahydrofuran (10ml) was added 2-thenoyl chloride (208mg) at 0°C, and the mixture was heated at 78°C overnight. After allowing to cool, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated, which was recrystallized from hexane-ethyl acetate to give methyl 7-bromo-1-(2-thienylcarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylate (236mg) as colorless crystals.

10  
15  
20  
25

$^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  2.98 (br, 2H), 3.82 (s, 3H), 6.73 (dd, 1H,  $J = 4.0, 1.0$  Hz), 6.80 - 6.85 (m, 1H), 6.91 (d, 1H, 8.8), 7.26 - 7.31 (m, 1H), 7.37 (dd, 1H,  $J = 5.2, 1.4$  Hz), 7.68 - 7.69 (m, 2H).

Anal. Calcd.  $C_{17}H_{14}NO_3Br$  Calcd. C, 52.05; H, 3.60; N, 3.57. Found C, 52.05; H, 3.45; N, 3.38.



## Reference Example 224

In toluene (10ml), ethanol (1.0ml) and water (1.0ml) were suspended methyl 7-bromo-1-(2-thienylcarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylate (210mg), 4-butoxyethoxyphenyl borate (166mg) and potassium carbonate (192mg), and the mixture was stirred for 30 minutes under argon atmosphere. Then, to the suspension was added tetrakis(triphenylphosphine)palladium (43mg), and the mixture was heated at 100°C for 5 hours under argon atmosphere. After allowing to cool, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give methyl 7-(4-butoxyethoxyphenyl)-1-(2-thienylcarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylate (201mg) as colorless oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.4 Hz), 1.30 - 1.45 (m, 2H), 1.50 - 1.65 (m, 2H), 3.00 (br, 2H), 3.56 (t, 2H, J = 7.0 Hz), 3.79 - 3.84 (m, 5H), 4.18 (t, 2H, J = 4.8 Hz), 6.74 - 6.82 (m, 2H), 7.02 (d, 2H, J = 8.8 Hz), 7.08 (d, 1H, J = 8.4 Hz), 7.32 - 7.40 (m, 2H), 7.54 (d, 2H, J = 8.8 Hz), 7.72 (d, 1H, J = 2.2 Hz), 7.83 (s, 1H).

## Reference Example 225

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-(2-thienylcarbonyl)--2,3-dihydro-1-benzazepine-4-carboxylate (200mg) in a mixture of tetrahydrofuran (12ml) and methanol (12ml) was added 1N sodium hydroxide solution (4ml), and the mixture was stirred at room temperature for 1 day. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-(2-thienylcarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (171mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (t, 3H, J = 7.4 Hz), 1.34 - 1.45 (m, 2H), 1.50 - 1.70 (m, 2H), 3.02 (br, 2H), 3.56 (t, 2H, J = 6.6 Hz), 3.82 (t, 2H, J = 4.4 Hz), 4.18 (t, 2H, J = 5.0 Hz), 6.72 - 6.83 (m, 2H), 7.02 (d, 2H, J = 8.8 Hz), 7.09 (d, 1H, J = 8.4 Hz), 7.34 - 7.42 (m, 2H), 7.54 (d, 2H, J = 8.8 Hz), 7.74 (d, 1H, J = 2.2 Hz), 7.92 (s, 1H).

Anal. Calcd. C<sub>28</sub>H<sub>29</sub>NO<sub>5</sub>S Calcd. C, 68.41; H, 5.95; N, 2.85. Found C, 68.18; H, 6.03; N, 2.84.

## Reference Example 226

To a suspension of 60% sodium hydride (2.3g) in

10018321-121201

tetrahydrofuran (40ml) which had been washed with hexane three times was added a solution of 4-bromopyrazole (7.0g) in tetrahydrofuran (40ml) at 0°C under nitrogen atmosphere, the temperature was returned room temperature, and the mixture was stirred for 1 hour. To this mixture was added dropwise a solution of ethyl iodide (8.9g) in tetrahydrofuran (30ml) at 0°C under nitrogen atmosphere, the temperature was returned to room temperature, and the mixture was stirred overnight. The solution was diluted with tetrahydrofuran, and the insolubles were filtered using Celite. The filtrate was concentrated under reduced pressure, hexane was added thereto, and the insolubles were filtered. The filtrate was concentrated under reduced pressure to give 4-bromo-1-ethylpyrazole (7.72g) as light yellow liquid.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.48 (t, 3H, J = 7.8 Hz), 4.16 (q, 2H, J = 7.4 Hz), 7.41 (s, 1H), 7.45 (s, 1H).

#### Reference Example 227

To a solution of 4-bromo-1-ethylpyrazole (7.0g) in dry tetrahydrofuran (150ml) was added dropwise n-butyllithium (30ml, 1.6M solution in hexane) at -78°C under nitrogen atmosphere. After 30 minutes, to the mixture was added dropwise DMF (14.6g) at -78°C under nitrogen atmosphere, the temperature was returned to room temperature, and the mixture was stirred for 1 hour.

Then, to the mixture was added 1N hydrochloric acid (60ml) at 0°C, and the mixture was stirred for 30 minutes, which was made basic with 1N sodium hydroxide solution, and the mixture was extracted with ethyl acetate five  
5 times. The extract was dried with magnesium sulfate, the solvent was evaporated under reduced pressure, and the resulting residue was subjected to silica gel column chromatography (hexane : ethyl acetate = 1 : 2) to give  
1-ethylpyrazole-4-carboxyaldehyde (2.9g) as light yellow  
10 oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.54 (t, 3H, J = 7.2 Hz), 4.24 (q, 2H, J = 7.4 Hz), 7.95 (s, 1H), 7.97 (s, 1H), 9.86 (s, 1H).

#### Reference Example 228

To a solution of methyl 7-(4-butoxyethoxyphenyl)-  
15 2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 1-ethylpyrazole-4-carboxyaldehyde (471mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxymethylborohydride (804mg), and the mixture was stirred under nitrogen atmosphere at room temperature for  
20 2 days. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified  
25 with silica gel column chromatography (hexane:ethyl

acetate=1:1) to give methyl 7-(4-butoxyethoxyphenyl)-1-  
[(1-ethylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-  
5-carboxylate (382mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.34 -  
5 1.70 (m, 7H), 2.76 (br, 2H), 3.27 (br, 2H), 3.56 (t, 2H, J  
= 6.6 Hz), 3.39 - 3.83 (m, 5H), 4.07 - 4.29 (m, 4H), 4.42  
(s, 2H), 6.94 - 7.00 (m, 3H), 7.33 - 7.54 (m, 6H), 7.79 (s,  
1H).

#### Reference Example 229

10 To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-  
[(1-ethylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-  
4-carboxylate (382mg) in a mixture of tetrahydrofuran  
(24ml) and methanol (24ml) was added 1N sodium hydroxide  
solution (8ml), and the mixture was stirred at room  
15 temperature for 1 day. Then, to the mixture was added  
water at 0°C, and 1N hydrochloric acid was further added  
to neutral, and the mixture was extracted with ethyl  
acetate. The organic layer was washed with water and  
saturated brine and dried with magnesium sulfate. The  
20 solvent was evaporated under reduced pressure, which was  
recrystallized from hexane-ethyl acetate to give 7-(4-  
butoxyethoxyphenyl)-1-[(1-ethylpyrazol-4-yl)methyl]-2,3-  
dihydro-1-benzazepine-4-carboxylic acid (287mg) as yellow  
crystals.

25 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.34 -

10018324-121201

1.65 (m, 7H), 2.78 (br, 2H), 3.29 (br, 2H), 3.56 (t, 2H, J = 6.6 Hz), 3.81 (t, 2H, J = 5.2 Hz), 4.11 - 4.22 (m, 4H), 4.44 (s, 2H), 6.95 - 7.01 (m, 3H), 7.34 (s, 1H), 7.41 - 7.50 (m, 4H), 7.56 (d, 1H, J = 2.2 Hz), 7.79 (s, 1H).

5 Anal. Calcd.  $C_{29}H_{35}N_3O_4$ , Calcd. C, 71.14; H, 7.21; N, 8.58. Found C, 70.84; H, 7.47; N, 8.48.

#### Reference Example 230

To a solution of ethyl 2-methyldioxolan-2-ylacetate (2.0g) in methanol (69ml) was added 1N sodium hydroxide  
10 solution (23ml), and the mixture was stirred at room temperature overnight. Then, the mixture was neutralized with 1N hydrochloric acid, and the solvent was evaporated under reduced pressure. To the mixture was added ethyl acetate, and the mixture was dried with magnesium sulfate.  
15 The solvent was evaporated under reduced pressure to give 2-methyldioxolan-2-ylacetic acid (1.63g) as colorless amorphous.

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.51 (s, 3H), 2.74 (s, 2H), 4.03 (s, 4H).

#### 20 Reference Example 231

To a solution of 5-(2-hydroxyethyl)-4-methylthiazole (2.5g) in dichloromethane (125ml) was added Celite (10.0g), and to the mixture was added PCC (18.9g), which  
was stirred for 2 hours under nitrogen atmosphere. The  
25 insolubles were filtered, followed by washing with ether.

The solvent was evaporated under reduced pressure, and the residue was subjected to Florisil column chromatography (ethyl acetate) to remove origin components, and the residue was recrystallized from  
5 hexane-ethyl acetate to give 4-methylthiazole-5-carboxyaldehyde (692mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.80 (s, 3H), 8.98 (s, 1H), 10.15 (s, 1H).

Reference Example 232

10 To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 4-methylthiazole-5-carboxyaldehyde (482mg) in 1,2-dichloroethane (15ml) was added sodium triacetoxymethylborohydride (804mg), and the mixture was  
15 stirred under nitrogen atmosphere at room temperature for 6 days. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under  
20 reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give methyl 7-(4-butoxyethoxyphenyl)-1-[(4-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-5-carboxylate (284mg) as yellow oil.

25 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.4 Hz), 1.34 -

10018331-121201

1.45 (m, 2H), 1.50 - 1.70 (m, 2H), 2.50 (s, 3H), 2.76 (t, 2H, J = 5.2 Hz), 3.26 (t, 2H, J = 5.2 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.78 - 3.83 (m, 5H), 4.16 (t, 2H, J = 4.4 Hz), 4.65 (s, 2H), 6.93 (d, 1H, J = 8.8 Hz), 6.98 (d, 2H, J = 9.2 Hz), 7.41 - 7.50 (m, 3H), 7.56 (d, 1H, J = 2.6 Hz), 7.78 (s, 1H), 8.66 (s, 1H).

#### Reference Example 233

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-[(4-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylate (284mg) in a mixture of tetrahydrofuran (18ml) and methanol (18ml) was added 1N sodium hydroxide solution (6ml), and the mixture was stirred at room temperature for 1 day. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(4-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (201mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.2 Hz), 1.30 - 1.50 (m, 2H), 1.50 - 1.70 (m, 2H), 2.51 (s, 3H), 2.79 (br, 2H), 3.29 (br, 2H), 3.56 (t, 2H, J = 6.6 Hz), 3.81 (t, 2H,



J = 4.8 Hz), 4.17 (t, 2H, J = 5.2 Hz), 4.67 (s, 2H), 6.92 - 7.01 (m, 3H), 7.43 - 7.50 (m, 3H), 7.58 (d, 1H, J = 2.6 Hz), 7.89 (s, 1H), 8.68 (s, 1H).

Anal. Calcd.  $C_{28}H_{32}N_2O_4$  Calcd. C, 68.27; H, 6.55; N, 5.69.

5 Found C, 67.95; H, 6.56; N, 5.63.

#### Reference Example 234

To a mixture (135.0g) of methyl 7-bromo-1-[(4-methylphenyl)sulfonyl]-oxo-2,3,4,5-tetrahydro-1-benzazepine-4-carboxylate and ethyl 7-bromo-1-[(4-methylphenyl)sulfonyl]-oxo-2,3,4,5-tetrahydro-1-benzazepine-4-carboxylate in tetrahydrofuran (1200ml) was added sodium borohydride (11.1g) at  $-65^{\circ}\text{C}$ , and to the mixture was added dropwise methanol (120ml). After completion of the addition, the mixture was stirred at  $-15^{\circ}\text{C}$  to  $25^{\circ}\text{C}$  for 1.5 hours, to the mixture was added dropwise acetone (67.8g, 1.17mol) at  $-25^{\circ}\text{C}$ , and the mixture was further stirred for 30 minutes. To the mixture were added ethyl acetate and water at  $-45^{\circ}\text{C}$ , which was separated, and the organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give brown oil (152.3g). The oil was dissolved in dry tetrahydrofuran (1000ml) as it was, and to the solution was added dropwise methanesulfonyl chloride (50.1g) at  $0^{\circ}\text{C}$  under nitrogen atmosphere. After completion of the

addition, the mixture was stirred at room temperature for 1 hour, and to the mixture was added dropwise DBU (66.6g), which was stirred for 5 hours. To the mixture was added water, the mixture was extracted with ethyl acetate, and the organic layer was washed with 1N hydrochloric acid twice and further with water and saturated brine, followed by drying with magnesium sulfate. The solvent was evaporated under reduced pressure to give brown oil (148g). This was dissolved in acetic acid (520ml), to the solution was added concentrated sulfuric acid (260ml, 4.88mol) at 0°C, and the mixture was heated at 90°C for 3 hours. After allowing to cool, to the mixture was added water (40ml), and the mixture was heated again at 90°C for 2.5 hours. After allowing to cool, the solvent was evaporated under reduced pressure. Ice was added to the resulting residue, and 6N sodium hydroxide solution was added to pH = 4. The precipitated solid was collected by filtration, and the solid was dissolved in 1N sodium hydroxide solution (1500ml). The insolubles were removed by filtration, 2N hydrochloric acid was added to the filtrate to adjust to pH = 4 at 0°C, and the precipitated solid was collected by filtration. The solid was dried under reduced pressure to give 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylic acid (69.4g) as green solid.

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 2.36 (t, 2H, J = 4.8 Hz), 2.87

(t, 2H, J = 4.8 Hz), 6.35 (d, 1H, J = 8.6, 2.6 Hz), 6.84 (dd, 1H, J = 8.6, 2.6 Hz), 7.08 (d, 1H, J = 2.6 Hz), 7.12 (s, 1H).

#### Reference Example 235

5 To a suspension of 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylic acid (68.2g) in methanol (100ml) was added concentrated sulfuric acid (37.3g) at 0°C, and the mixture was heated at 80°C for 10 hours. After allowing to cool, the solvent was evaporated under  
10 reduced pressure. Ethyl acetate and water were added thereto and 1N sodium hydroxide solution was added to pH=4 at 0°C. The solution was separated, and the organic phase was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under  
15 reduced pressure, the resulting residue was subjected to silica gel column to remove origin components (ethyl acetate), and the resulting solid was washed with diisopropyl ether to give methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (44.0g). The filtrate was  
20 purified with silica gel column (hexane : ethyl acetate = 4 : 1) to give methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (3.4g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.86 (t, 2H, J = 5.2 Hz), 3.36 (t, 2H, J = 5.2 Hz), 3.80 (s, 3H), 4.57 (br, 1H), 6.49 (d, 1H, J = 8.4 Hz), 7.15 (dd, 1H, J = 8.4, 2.2 Hz), 7.38 (d, 1H, J

= 2.2 Hz), 7.53 (s, 1H).

Reference Example 236

*Amen.*  
*B50*

In toluene (100ml), ethanol (10ml) and water (10ml) were suspended methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (3.0g), 4-propoxyethoxyphenyl borate (3.1g) and potassium carbonate (3.8g), and the suspension was stirred for 30 minutes under argon atmosphere. Then, to the suspension was added tetrakis(triphenylphosphine)palldium (860mg), and the mixture was heated at 100°C for 8 hours under argon atmosphere. After allowing to cool, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give the solid, which was washed with hexane to give methyl 7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (2.59g) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.2 Hz), 1.56 - 1.74 (2H, m), 2.88 (2H, t, J = 4.8 Hz), 3.41 (2H, t, J = 4.8 Hz), 3.51 (2H, t, J = 7.0 Hz), 3.78 - 3.83 (m, 5H), 4.16 (2H, t, J = 4.8 Hz), 6.66 (1H, d, J = 8.0 Hz), 6.97 (2H, d, J = 6.68 Hz), 7.31 (1H, dd, J = 8.0, 2.2 Hz), 7.43

- 7.47 (3H, m), 7.725 (1H, s).

Reference Example 237

In toluene (200ml) and ethanol (35ml) were suspended methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (5.0g), 4-butoxyphenyl borate (4.6g) and 1M potassium carbonate solution (35ml), and the mixture was stirred for 30 minutes under argon atmosphere. Then, to the mixture was added tetrakis(triphenylphosphine)palladium (1.0g), and the mixture was heated at 100°C overnight under argon atmosphere. After allowing to cool, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to give the solid, which was washed with hexane to give methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (5.7g) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.3 Hz), 1.29 - 1.49 (2H, m), 1.55 - 1.68 (2H, m), 2.86 - 2.95 (2H, m), 3.41 - 3.45 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.68 (1H, d, J = 8.6 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.34 (1H, d, J = 8.6, 2.0 Hz), 7.43 - 7.48 (3H, m), 7.85 (1H, s).

Amn.  
B51

100183321.121201

$C_{23}H_{27}NO_4$  Calcd. C, 72.42; H, 7.13; N, 3.67. Found C, 72.32; H, 7.01; N, 3.84.

Reference Example 238

To a suspension of 60% sodium hydride (4.2g) in  
5 tetrahydrofuran (40ml) which had been washed with hexane  
three times was added dropwise a solution of 4-  
bromopyrazole (7.0g) in tetrahydrofuran (50ml) at 0°C  
under nitrogen atmosphere, the temperature was returned  
to room temperature, and the mixture was stirred for 1  
10 hour. To the mixture was added dropwise a solution of  
ethyl iodide (17.8g) in tetrahydrofuran (30ml) at 0°C  
under nitrogen atmosphere and the mixture was refluxed  
for 1 day. The solution was diluted with tetrahydrofuran,  
and the insolubles were filtered using Celite. After the  
15 filtrate was concentrated under reduced pressure, hexane  
was further added, and the insolubles were removed by  
filtration. The filtrate was concentrated under reduced  
pressure, followed by distillation under reduced pressure  
to give 4-bromo-1-isopropylpyrazole (5.8g) as light  
20 yellow liquid.

$^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  1.50 (d, 6H,  $J = 6.6$  Hz), 4.40 -  
4.54 (m, 1H), 7.43 (s, 1H), 7.45 (s, 1H).

Reference Example 239

To a solution of 4-bromo-1-isopropylpyrazole (5.0g)  
25 in dry ether (75ml) was added dropwise n-butyllithium

10018321.121201

(22ml, 1.6M solution in hexane) at -78°C under nitrogen atmosphere. After 30 minutes, to the mixture was added dropwise DMF (9.7g) at -78°C under nitrogen atmosphere, the temperature was returned to room temperature and the mixture was stirred for 1 hour. Then, to the mixture was added 1N hydrochloric acid (40ml) at 0°C, and the mixture was stirred for 30 minutes, made basic with 1N sodium hydroxide solution, extracted with ethyl acetate five times and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give 1-isopropylpyrazole-4-carboxyaldehyde (3.6g) as light yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.55 (d, 6H, J = 6.6 Hz), 4.48 - 4.61 (m, 1H), 7.98 (s, 2H), 9.86 (s, 1H).

15 Reference Example 240

To a solution of methyl 7-(4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (300mg) and 1-isopropylpyrazole-4-carboxyaldehyde (524mg) in 1,2-dichloroethane (10ml) was added sodium triacetoxymethylborohydride (964mg), and the mixture was stirred under nitrogen atmosphere at room temperature for 4 days. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under

reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 3 : 1) to give methyl 7-(4-butoxyethoxyphenyl)-1-[(1-isopropylpyrazol-4-yl)methyl]-2,3-dihydro-1-

5 benzazepine-5-carboxylate (392mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.34 - 1.65 (m, 10H), 2.75 (t, 2H, J = 5.0 Hz), 3.26 (t, 2H, J = 5.0 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.78 - 3.83 (m, 5H), 4.16 (t, 2H, J = 4.8 Hz), 4.42 (s, 2H), 4.44 - 4.61 (m, 1H),  
10 6.94 - 7.00 (m, 3H), 7.36 - 7.50 (m, 5H), 7.55 (d, 1H, J = 2.6 Hz), 7.79 (s, 1H).

#### Reference Example 241

To a solution of methyl 7-(4-butoxyethoxyphenyl)-1-[(1-ethylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-  
15 4-carboxylate (392mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 3 days. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added  
20 to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-  
25 butoxyethoxyphenyl)-1-[(1-isopropylpyrazol-4-yl)methyl]-



2,3-dihydro-1-benzazepine-4-carboxylic acid (229mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (t, 3H, J = 7.0 Hz), 1.34 - 1.45 (m, 2H), 1.50 (d, 6H, J = 6.6 Hz), 1.53 - 1.68 (m, 2H),  
5 2.77 (br, 2H), 3.29 (br, 2H), 3.56 (t, 2H, J = 6.6 Hz),  
3.81 (t, 2H, J = 5.2 Hz), 4.16 (t, 2H, J = 5.0 Hz), 4.43 - 4.52 (m, 3H), 6.96 - 7.00 (m, 3H), 7.36 - 7.55 (m, 6H), 7.89 (s, 1H).

Anal. Calcd. C<sub>30</sub>H<sub>37</sub>N<sub>3</sub>O<sub>4</sub> Calcd. C, 71.54; H, 7.40; N, 8.34.  
10 Found C, 71.16; H, 7.24; N, 8.23.

#### Reference Example 242

To a solution of methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (800mg) and 1-ethylpyrazole-4-carboxyaldehyde (1.05g) in 1,2-dichloroethane (30ml) were  
15 added sodium triacetoxymethylborohydride (3.0g) and acetic acid (853mg) and the mixture was stirred under nitrogen atmosphere at room temperature for 2 days. Then, water was added to the mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with  
20 saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give  
methyl 7-bromo-1-[(1-ethylpyrazol-4-yl)methyl]-2,3-  
25 dihydro-1-benzazepine-5-carboxylate (593mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.48 (t, 3H, J = 6.6 Hz), 2.73 (t, 2H, J = 4.8 Hz), 3.22 (t, 2H, J = 4.8 Hz), 3.80 (s, 3H), 4.15 (q, 2H, J = 7.4 Hz), 4.36 (s, 2H), 6.77 (d, 1H, J = 8.8 Hz), 7.22 - 7.29 (m, 2H), 7.42 (s, 1H), 7.45 (d, 1H, J = 2.2 Hz), 7.60 (s, 1H).

Reference Example 243

In toluene (15ml), ethanol (1.5ml) and water (1.5ml) were suspended methyl 7-bromo-1-[(1-ethylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylate (550mg), 4-propoxyethoxyphenyl borate (320mg) and potassium carbonate (506mg), and the suspension was stirred for 30 minutes under argon atmosphere. Then, to the suspension was added tetrakis(triphenylphosphine)palladium (81mg), and the mixture was heated at 100°C for 6 hours under argon atmosphere. After allowing to cool, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane : ethyl acetate = 1 : 1) to give methyl 1-[(1-ethylpyrazol-4-yl)methyl]-7-(4-propoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (370mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.06 (t, 3H, J = 7.6 Hz), 1.48 (t, 3H, J = 7.4 Hz), 1.75 - 1.95 (m, 2H), 2.76 (t, 2H, J = 5.4

Ammon.  
B52

10018321.121201

Hz), 3.27 (t, 2H, J = 5.4 Hz), 3.81 (s, 3H), 3.96 (t, 2H, J = 6.6 Hz), 4.16 (q, 2H, J = 7.4 Hz), 4.42 (s, 2H), 6.93 - 6.97 (m, 3H), 7.33 (s, 1H), 7.38 - 7.49 (m, 4H), 7.54 (d, 1H, J = 2.4 Hz), 7.79 (s, 1H).

5           Reference Example 244

To a solution of methyl 1-[(1-ethylpyrazol-4-yl)methyl]-7-(4-propoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (370mg) in a mixture of tetrahydrofuran (24ml) and methanol (24ml) was added 1N sodium hydroxide solution (8ml), and the mixture was stirred at room temperature for 1 day. Then, to the mixture was added water at 0°C, and 1N hydrochloric acid was further added to neutral, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give 1-[(1-ethylpyrazol-4-yl)methyl]-7-(4-propoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (330mg) as yellow oil.

20   <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.06 (t, 3H, J = 7.6 Hz), 1.49 (t, 3H, J = 7.4 Hz), 1.78 - 1.89 (m, 2H), 2.78 (br, 2H), 3.30 (br, 2H), 3.96 (t, 2H, J = 6.6 Hz), 4.16 (q, 2H, J = 7.4 Hz), 4.44 (s, 2H), 6.93 - 6.99 (m, 3H), 7.34 (s, 1H), 7.40 - 7.50 (m, 4H), 7.56 (d, 1H, J = 2.2 Hz), 7.89 (s, 1H).

25           Reference Example 245

Amen.  
B53

In methanol (25ml) and THF (10ml) was dissolved methyl 7-[(4-(2-butoxyethoxy)phenyl)-1-(2-methylthiazol-4-yl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.17g). To the solution was added 1N sodium hydroxide solution (4ml), and the mixture was stirred at room temperature overnight, heated at 60°C for 5 hours, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-[(4-(2-butoxyethoxy)phenyl)-1-(2-methylthiazol-4-yl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.12g) as yellow crystals.

mp 155 - 158°C.

<sup>1</sup>H-NMR (δ ppm, CDCl<sub>3</sub>) 0.94 (3H, t, J = 7.2 Hz), 1.31 - 1.49 (2H, m), 1.55 - 1.69 (2H, m), 2.67 (3H, s), 2.87 (2H, t-like), 3.56 (2H, t, J = 6.6 Hz), 3.82 (2H, t, J = 4.9 Hz), 3.96 (2H, t-like), 4.17 (2H, t, J = 4.9 Hz), 5.97 (1H, s), 7.00 (2H, d, J = 8.6 Hz), 7.44 (2H, s), 7.51 (2H, d, J = 8.6 Hz), 7.63 (1H, s), 7.88 (1H, s).

IR (KBr) v: 2926, 1674, 1530, 1495 cm<sup>-1</sup>.

#### Reference Example 246

In THF (6.0ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylate (0.30g). To the solution was added 60%

1001831.121201

10018324-121201

sodium hydride (61mg) under ice-cooling and the mixture was stirred at room temperature for 1 hour. To the mixture was added crotyl bromide (0.31ml), and the mixture was stirred at 60°C for 4 days. After cooled to room temperature, the reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 4/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-crotyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.23g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.33 - 1.45 (2H, m), 1.54 - 1.65 (2H, m), 1.75 (3H, d, J = 5.2 Hz), 2.71 - 2.82 (2H, m), 3.22 - 3.27 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.77 - 3.82 (2H, m), 3.81 (3H, s), 3.88 (2H, d, J = 4.4 Hz), 5.22 (1H, m), 5.63 (1H, m), 6.85 - 7.01 (3H, m), 7.36 - 7.49 (4H, m), 7.77 (1H, s).

#### 20 Reference Example 247

In THF (4.4ml)/methanol (4.4ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-crotyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.22g). To the solution was added 1N sodium hydroxide solution (2.2ml), and the mixture was stirred at 40°C for 6 hours. pH was adjusted

to approximate 5 with 1N hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate=8/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-crotyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (198mg).

10 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.34 - 1.45 (2H, m), 1.54 - 1.65 (2H, m), 1.76 (3H, d, J = 5.4 Hz), 2.82 (2H, m), 3.27 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.78 - 3.83 (2H, m), 3.89 (3H, s), 4.13 - 4.18 (2H, m), 5.23 (1H, m), 5.66 (1H, m), 6.88 (1H, d, J = 6.2 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.38 - 7.53 (4H, m), 7.88 (1H, s).

#### Working Example 83 (Production of Compound 83)

In DMF (3.9ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-crotyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.20g). To the solution was added thionyl chloride (82μl), and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, and a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (111mg) and triethylamine (0.31ml) in THF (3.3ml) under

ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 4/1), which was recrystallized from isopropyl ether/ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-1-crotyl-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 83) (9mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.25 - 1.45 (2H, m), 1.53 - 1.78 (6H, m), 2.20 (3H, s), 2.68 (1H, m), 3.33 - 3.43 (4H, m), 3.55 (2H, t, J = 7.0 Hz), 3.59 (2H, s), 3.77 - 3.80 (2H, m), 3.88 (2H, m), 3.98 - 4.07 (2H, m), 4.12 - 4.18 (2H, m), 5.24 (1H, m), 5.62 (1H, m), 6.68 (3H, s), 6.90 (1H, d, J = 8.4 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.27 - 7.58 (7H, m).

Reference Example 248

Methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (2.0g) was dissolved in 1,2-dichloroethane (70ml). To the solution were added isobutylaldehyde (3.2ml) and sodium triacetoxyborohydride (5.26g), and the mixture was stirred at room temperature for 12 hours.

The solvent was removed under reduced pressure, and the resulting residue was added to water and extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 6/1) to give methyl 7-bromo-1-isobutyl-2,3-dihydro-1-benzazepine-4-carboxylate (1.82g). <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.92 (6H, d, J = 6.6 Hz), 2.03 (1H, m), 2.77 - 2.82 (2H, m), 3.10 (2H, d, J = 7.4 Hz), 3.21 - 3.26 (2H, m), 3.80 (3H, s), 6.71 (1H, d, J = 8.8 Hz), 7.19 - 7.26 (1H, m), 7.42 (1H, d, J = 2.6 Hz), 7.58 (1H, s).

Reference Example 249

In toluene/ethanol/water (= 10/1/1, 41ml) was dissolved methyl 7-bromo-1-isobutyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.90g). To the solution were added 4-(2-propoxyethoxy)phenyl borate (0.72g) and potassium carbonate (0.81g) and the mixture was stirred for 30 minutes under argon atmosphere. To the mixture was added tetrakis(triphenylphosphine)palladium (123mg), and the mixture was heated to reflux for 14 hours. After cooled to room temperature, the solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried with magnesium sulfate. The solvent was removed under

10018321131201

Amer.  
B54



reduced pressure, and the resulting residue was purified  
with silica gel column chromatography (hexane/ethyl  
acetate = 8/1) to give methyl 1-isobutyl-7-[4-(2-  
propoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-  
5 carboxylate (0.79g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.2 Hz), 0.95 (6H,  
d, J = 6.6 Hz), 1.57 - 1.72 (2H, m), 1.98 - 2.15 (1H, m),  
2.80 - 2.85 (2H, m), 3.16 (2H, d, J = 7.2 Hz), 3.27 - 3.32  
(2H, m), 3.51 (2H, t, J = 6.6 Hz), 3.78 - 3.83 (2H, m),  
10 3.81 (3H, s), 4.13 - 4.19 (2H, m), 6.89 (1H, d, J = 8.8 Hz),  
6.95 - 7.00 (2H, m), 7.39 (1H, dd, J = 8.8, 2.2 Hz), 7.43 -  
7.49 (3H, m), 7.77 (1H, s).

IR (KBr) 2961, 2870, 1701, 1607, 1499, 1248, 1180, 927, 820  
cm<sup>-1</sup>.

15 Reference Example 250

In THF (15.8ml)/methanol (15.8ml) was dissolved  
methyl 1-isobutyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-  
dihydro-1-benzazepine-4-carboxylate (0.79g). To the  
solution was added 1N sodium hydroxide solution (7.9ml)  
20 and the mixture was stirred at room temperature for 20  
hours. pH was adjusted to approximate 4 with 1N  
hydrochloric acid, and the solvent was concentrated to  
half under reduced pressure. The concentrated material  
was extracted with ethyl acetate, and the extract was  
25 washed with saturated brine and dried with magnesium

10018321.121201

sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (= 6/1) to give 1-isobutyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.57g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J = 7.2 Hz), 0.96 (6H, d, J = 6.6 Hz), 1.59 - 1.71 (2H, m), 2.00 - 2.17 (1H, m), 2.80 - 2.86 (2H, m), 3.19 (2H, d, J = 7.2 Hz), 3.30 - 3.35 (2H, m), 3.52 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 4.8 Hz), 4.17 (2H, t, J = 4.8 Hz), 6.90 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.38 - 7.53 (4H, m), 7.89 (1H, s).

Working Example 84 (Production of Compound 84)

In THF (11.4ml) was dissolved 1-isobutyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.57g). To the solution was added oxalyl chloride (0.23ml), and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (0.33g) and triethylamine (0.94ml) in THF (9.9ml) under ice-cooling, and the mixture was stirred at room temperature for 14 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and

dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 4/1), which was recrystallized from  
 5 hexane/ethyl acetate to give 1-isobutyl-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 84) (0.56g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.2 Hz), 0.97 (6H, d, J = 6.6 Hz), 1.62 - 1.82 (6H, m), 2.00 - 2.17 (1H, m), 2.20 (3H, s), 2.64 (1H, m), 2.87 - 2.95 (2H, m), 3.18 (2H, d, J = 7.4 Hz), 3.30 - 3.43 (4H, m), 3.51 (2H, t, J = 7.0 Hz), 3.56 (2H, s), 3.78 - 3.83 (2H, m), 3.99 - 4.07 (2H, m), 4.13 - 4.19 (2H, m), 6.91 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.27 - 7.57 (10H, m).  
 10  
 15

IR (KBr) 3303, 2957, 1636, 1607, 1499, 1244, 1122, 926, 812 cm<sup>-1</sup>.

Anal. Calcd. C<sub>39</sub>H<sub>51</sub>N<sub>3</sub>O<sub>4</sub> Calcd. C, 74.85; N, 6.71; H, 8.21. Found C, 74.69; N, 6.92; H, 8.34.

20 Reference Example 251

Methyl 7-bromo-1-isobutyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.90g) was dissolved in toluene/ethanol/water (=10/1/1, 41ml). To the solution were added 4-(2-butoxyethoxy)phenyl borate (0.76g) and  
 25 potassium carbonate (0.18g), and the mixture was stirred

under argon atmosphere for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium (123mg), and the mixture was heated to reflux for 14 hours. After cooled to room temperature, the reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate=8/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-isobutyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.75g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 0.95 (6H, d, J = 6.6 Hz), 1.37 - 1.67 (4H, m), 2.26 (1H, m), 2.82 (2H, m), 3.17 (2H, d, J = 4.8 Hz), 3.30 (2H, t, J = 4.8 Hz), 3.55 (2H, t, J = 6.6 Hz), 3.77 - 3.83 (2H, m), 3.81 (3, s), 4.13 - 4.18 (2H, m), 6.89 (1H, d, J = 8.4 Hz), 6.94 - 7.00 (2H, m), 7.36 - 7.52 (4H, m), 7.77 (1H, s).

IR (KBr) 2959, 1703, 1607, 1499, 1244, 1181, 814 cm<sup>-1</sup>.

#### Reference Example 252

In THF (15.0ml)/methanol (15.0ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-isobutyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.75g). To the solution was added 1N sodium hydroxide solution (7.5ml), and the mixture was stirred at room temperature for 20

hours. pH was adjusted to approximate 4 with 1N hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (= 6/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-isobutyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.61g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.0 Hz), 0.96 (6H, d, J = 6.6 Hz), 1.34 - 1.47 (2H, m), 1.54 - 1.66 (2H, m), 2.08 (1H, m), 2.79 - 2.85 (2H, m), 3.19 (2H, d, J = 6.8 Hz), 3.30 - 3.35 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 4.8 Hz), 4.16 (2H, J = 4.8 Hz), 6.90 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.38 - 7.53 (4H, m), 7.89 (1H, s).

Working Example 85 (Production of Compound 85)

In THF (12.0ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-isobutyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.60g). To the solution was added oxalyl chloride (0.24ml), and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline

(0.33g) and triethylamine (0.96ml) in THF (9.6ml) under ice-cooling, and the mixture was stirred at room temperature for 14 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 4/1), which was recrystallized from hexane/ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-1-isobutyl-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 85) (0.49g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.97 (6H, d, J = 6.6 Hz), 1.33 - 1.46 (2H, m), 1.54 - 1.77 (6H, m), 2.07 (1H, m), 2.20 (3H, s), 2.64 (1H, m), 2.88 - 2.95 (2H, m), 3.18 (2H, d, J = 7.4 Hz), 3.30 - 3.43 (4H, m), 3.51 - 3.59 (2H, m), 3.56 (2H, s), 3.77 - 3.83 (2H, m), 3.98 - 4.07 (2H, m), 4.12 - 4.18 (2H, m), 6.91 (1H, d, J = 8.8 Hz), 6.99 (2H, d, J = 8.4 Hz), 7.29 (1H, d, J = 8.4 Hz), 7.36 - 7.58 (9H, m).

IR (KBr) 3303, 2955, 1636, 1597, 1499, 1242, 1121, 926, 812 cm<sup>-1</sup>.

Anal. Calcd. C<sub>40</sub>H<sub>53</sub>N<sub>3</sub>O<sub>4</sub> Calcd. C, 75.08; N, 6.57; H, 8.35. Found C, 74.99; N, 6.69; H, 8.16.

## Reference Example 253

10018321.121201

In 1,2-dichloroethane (60ml) was dissolved methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (1.7g). To the solution were added isopentylaldehyde (3.1g) and sodium triacetoxymethylborohydride (4.5g), and the mixture was stirred at room temperature for 12 hours. The solvent was removed under reduced pressure, and the resulting residue was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 5/1) to give methyl 7-bromo-1-isopentyl-2,3-dihydro-1-benzazepine-4-carboxylate (1.84g).

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.95 (6H, d,  $J = 6.2$  Hz), 1.48 - 1.62 (3H, m), 2.79 (2H, t,  $J = 4.4$  Hz), 3.21 (2H, t,  $J = 4.4$  Hz), 3.24 - 3.33 (2H, m), 3.80 (3H, s), 6.68 (1H, d,  $J = 8.8$  Hz), 7.20 - 7.26 (1H, m), 7.41 (1H, d,  $J = 2.2$  Hz), 7.56 (1H, s).

## Reference Example 254

In THF (36ml)/methanol (36ml) was dissolved methyl 7-bromo-1-isopentyl-2,3-dihydro-1-benzazepine-4-carboxylate (1.8g). To the solution was added 1N sodium hydroxide solution (18ml), and the mixture was stirred at

room temperature for 24 hours. pH was adjusted to approximate 5 with 1N hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (= 6/1) to give 7-bromo-1-isopentyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (1.51g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.96 (6H, d, J = 6.2 Hz), 1.52 - 1.71 (3H, m), 2.78 - 2.84 (2H, m), 3.21 - 3.26 (2H, m), 3.32 (2H, d, J = 8.2 Hz), 6.69 (1H, d, J = 8.8 Hz), 7.22 - 7.29 (1H, m), 7.43 (1H, d, J = 2.2 Hz), 7.68 (1H, s).

#### Reference Example 255

In DMF (30ml) was dissolved 7-bromo-1-isopentyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (1.5g). To the solution was added thionyl chloride (0.84ml), and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (1.04g) and triethylamine (3.2ml) in THF (20.8ml) under ice-cooling, and the mixture was stirred at room temperature for 16 hours. The reaction solution was added to water, and the mixture was



extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1) to give 7-bromo-1-isopentyl-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (1.35g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.96 (6H, d, J = 6.2 Hz), 1.54 - 1.86 (5H, m), 2.21 (3H, s), 2.66 (1H, m), 2.88 (2H, m), 3.26 (2H, m), 3.28 - 3.44 (2H, m), 3.57 (2H, s), 3.98 - 4.11 (2H, m), 6.70 (1H, d, J = 8.8 Hz), 7.18 - 7.40 (3H, m), 7.54 (2H, d, J = 8.4 Hz), 7.64 (1H, s), 8.02 (1H, s).

Working Example 86 (Production of Compound 86)

In toluene/ethanol/water (=10/1/1, 31.5ml) was dissolved 7-bromo-1-isopentyl-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (0.66g). To the solution were added 4-(2-propoxyethoxy)phenyl borate (0.33g) and potassium carbonate (0.37g), and the mixture was stirred for 30 minutes under argon atmosphere. To the mixture was added tetrakis(triphenylphosphine)palladium (56mg), and the mixture was heated to reflux for 16 hours. After cooled to room temperature, the reaction solution was added to water, and the mixture was extracted with ethyl

acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl

5 acetate/ethanol = 3/1). The purified residue was dissolved in ethyl acetate and filtered to give a solution. The solvent was removed under reduced pressure, followed by recrystallization from isopropyl ether/ethyl acetate to give 1-isopentyl-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 86) (80mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.4 Hz), 0.96 (6H, d, J = 6.0 Hz), 1.54 - 1.76 (6H, m), 2.21 (3H, s), 2.68 (1H, m), 2.89 (2H, m), 3.30 - 3.50 (9H, m), 3.51 (2H, t, J = 6.2 Hz), 3.58 (2H, s), 3.98 - 4.07 (2H, m), 4.15 (2H, t, J = 4.8 Hz), 6.65 (1H, s), 6.70 - 6.81 (1H, m), 6.88 (1H, d, J = 9.2 Hz), 6.96 (2H, d, J = 8.6 Hz), 7.30 - 7.69 (9H, m).

IR (KBr) 3312, 2953, 2867, 1644, 1605, 1501, 1244, 829 cm<sup>-1</sup>.

20 Working Example 87 (Production of Compound 87)

In toluene/ethanol/water (=10/1/1, 31.5ml) was dissolved 7-bromo-1-isopentyl-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (0.66g). To the solution were added 4-(2-butoxyethoxy)phenyl borate (0.35g) and

25

potassium carbonate (0.37g), and the mixture was stirred for 30 minutes under argon atmosphere. To the mixture was added tetrakis(triphenylphosphine)palladium (56mg), and the mixture was heated to reflux for 16 hours. After  
5 cooled to room temperature, the reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was  
10 purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1). The purified residue was dissolved in ethyl acetate and filtered to give a solution. The solvent was removed under reduced pressure, followed by recrystallization from isopropyl ether/ethyl  
15 acetate to give 7-[4-(2-butoxyethoxy)phenyl]-1-isopentyl-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 87) (74mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 0.98 (6H, d, J = 6.2 Hz), 1.33 - 1.45 (2H, m), 1.54 - 1.75 (6H, m),  
20 2.21 (3H, s), 2.67 (1H, m), 2.85 - 2.92 (2H, m), 3.30 - 3.43 (9H, m), 3.55 (2H, t, J = 6.6 Hz), 3.58 (2H, s), 3.77 - 3.83 (2H, m), 4.00 - 4.06 (2H, m), 4.12 - 4.17 (2H, m),  
6.66 (1H, s), 6.89 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J =  
25 8.8 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.38 - 7.63 (7H, m).

IR (KBr) 3328, 2957, 2870, 1642, 1607, 1503, 1242, 1140, 823  $\text{cm}^{-1}$ .

Reference Example 256

In THF (14.0ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylate (0.70g). To the solution was added 60% sodium hydride (142mg) at 0°C, and the mixture was stirred at room temperature for 1 hour. To the mixture was added 1-bromo-3-methyl-2-butene (0.83ml), and the mixture was stirred at 60°C for 60 hours. After cooled to room temperature, the mixture was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl/acetate = 4/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(3-methyl-2-butenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.71g).

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (3H, d,  $J = 7.2$  Hz), 1.33-1.45 (2H, m), 1.54 - 1.68 (2H, m), 1.75 (3H, s), 1.78 (3H, s), 2.78 - 2.83 (2H, m), 3.19 - 3.25 (2H, m), 3.55 (2H, t,  $J = 6.6$  Hz), 3.77 - 3.80 (2H, m), 3.93 (2H, d,  $J = 6.2$  Hz), 4.10 - 4.18 (2H, m), 5.32 (1H, m), 6.86 (1H, d,  $J = 8.4$  Hz), 6.97 (2H, d,  $J = 8.8$  Hz), 7.37 - 7.52 (4H, m), 7.76 (1H, s).

## Reference Example 257

In THF (14.0ml)/methanol (14.0ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(3-methyl-2-butenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.70g).

5 To the solution was added 1N sodium hydroxide (7.0ml), and the mixture was stirred at room temperature for 24 hours. pH was adjusted to approximate 4 with 1N hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material  
10 was extracted with ethyl acetate, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (= 6/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-  
15 (3-methyl-2-butenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.46g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, d, J = 7.2 Hz), 1.35 - 1.47 (2H, m), 1.54 - 1.65 (2H, m), 1.76 (3H, s), 1.79 (3H, s), 2.79 - 2.85 (2H, m), 3.21 - 3.29 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.78 - 3.83 (2H, m), 3.95 (2H, d, J = 5.8 Hz),  
20 4.13 - 4.19 (2H, m), 5.33 (1H, m), 6.87 (1H, d, J = 8.4 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.38 - 7.54 (2H, m), 7.47 (2H, d, J = 8.8 Hz), 7.89 (1H, s).

## Working Example 88 (Production of Compound 88)

25 In THF (9.0ml) was dissolved 7-[4-(2-

10018321-121001

butoxyethoxy)phenyl]-1-(3-methyl-2-butenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.40g). To the solution was added oxalyl chloride (0.18ml), and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (0.24g) and triethylamine (0.70ml) in THF (7.2ml) under ice-cooling, and the mixture was stirred at room temperature for 14 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 4/1), which was recrystallized from hexane/ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-1-isobutyl-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 88) (0.33g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, d, J = 7.2 Hz), 1.33 - 1.45 (2H, m), 1.54 - 1.67 (6H, m), 1.77 (3H, s), 1.80 (3H, s), 2.21 (3H, m), 2.65 (1H, m), 2.91 (2H, m), 3.25 - 3.44 (4H, m), 3.55 (2H, t, J = 6.6 Hz), 3.57 (2H, s), 3.80 (2H, t, J = 4.8 Hz), 3.95 (2H, d, J = 6.2 Hz), 4.00 - 4.08 (2H,

10018321.121201

m), 4.16 2H, t,  $J = 4.6$  Hz), 5.34 (1H, m), 6.89 (1H, d,  $J = 8.8$  Hz), 6.97 (2H, d,  $J = 8.8$  Hz), 7.27 - 7.56 (10H, m).

IR (KBr) 2926, 2865, 1703, 1607, 1499, 1244, 1181, 814  $\text{cm}^{-1}$ .

Anal. Calcd.  $\text{C}_{41}\text{H}_{53}\text{N}_3\text{O}_4$  Calcd. C, 75.54; N, 6.45; H, 8.19.

5 Found C, 75.39; N, 6.40; H, 8.03.

Reference Example 258

In THF (228ml) was dissolved 2-ethoxyethanol (22.8g). To the solution were added triethylamine (49.3ml) and methanesulfonyl chloride (23.6ml) at  $0^\circ\text{C}$ , and the mixture  
10 was stirred at room temperature for 1 hour. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the  
15 resulting residue was added dropwise to a solution of 4-[(benzyloxycarbonyl)amino]butyric acid (30.0g) and 60% sodium hydride (10.1g) in THF (450ml). The mixture was stirred at  $60^\circ\text{C}$  for 16 hours, cooled to room temperature, and the reaction solution was added to water. To the  
20 mixture was added 1N sodium hydroxide (50ml), and the mixture was washed with ethyl acetate. The mixture was neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated sodium thiosulfate solution and dried with magnesium  
25 sulfate. The solvent was removed under reduced pressure,

and the resulting residue was dissolved in methylene chloride (54.6ml), which was added dropwise to a solution of concentrated sulfuric acid (8.23ml) and magnesium sulfate (28.3g) in methylene chloride (273ml). To the mixture was added 2-methyl-2-propanol (28.1ml), and the mixture was stirred at room temperature for 18 hours. To the mixture was added an aqueous solution of sodium hydrogen carbonate to adjust pH to approximate 8, and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated brine, and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 6/1 → 5/1) to give tert-butyl 4-[(benzyloxycarbonyl)(2-ethoxyethyl)amino]butyrate (8.7g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.20 (3H, d, J = 7.4 Hz), 1.44 (9H, s), 1.71 - 1.82 (2H, m), 2.27 (2H, t, J = 7.2 Hz), 2.64 (2H, t, J = 7.4 Hz), 2.72 - 2.81 (2H, m), 3.50 (2H, q, J = 7.4 Hz), 3.50 - 3.56 (2H, m).

#### Reference Example 259

In methanol (87ml) was dissolved tert-butyl 4-[(benzyloxycarbonyl)(2-ethoxyethyl)amino]butyrate (8.7g). To the solution was added 10% palladium/carbon (0.87g), and the mixture was stirred for 3 hours under hydrogen atmosphere. 10% palladium/carbon was removed by



filtration with Celite, and the solvent of the resulting solution was removed under reduced pressure to give tert-butyl 4-[(2-ethoxyethyl)amino]butyrate (5.5g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.26 (3H, d, J = 7.0 Hz), 1.43 (9H, s), 1.77 - 1.87 (2H, m), 2.18 - 2.27 (2H, m), 3.31 - 3.57 (6H, m), 5.13 (2H, s), 7.32 - 7.37 (5H, m).

Reference Example 260

In DMF (43.9ml) was dissolved tert-butyl 4-[(2-ethoxyethyl)amino]butyrate (5.5g). To the solution was added 5-bromo-2-fluorobenzaldehyde (4.4g), followed by addition of potassium carbonate (3.6g). The mixture was stirred at 90°C for 60 hours and cooled to room temperature. The reaction solution was added to water, the mixture was extracted with ethyl acetate, washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 6/1 → 5/1) to give tert-butyl 4-[4-bromo(2-ethoxyethyl)-2-formylanilino]butyrate (2.3g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.12 (3H, d, J = 7.0 Hz), 1.41 (9H, s), 1.76 - 1.81 (2H, m), 2.16 - 2.24 (2H, m), 3.23 (2H, t, J = 7.4 Hz), 3.28 - 3.39 (4H, m), 3.37 (2H, q, J = 7.0 Hz), 3.43 - 3.49 (2H, m), 7.14 (1H, d, J = 8.6 Hz), 7.59 (1H, dd, J = 8.8, 2.6 Hz), 7.91 (1H, d, J = 2.4 Hz), 10.30 (1H, s).

## Reference Example 261

In toluene (4.8ml)/2-methyl-2-propanol (0.48ml) was dissolved tert-butyl 4-[4-bromo(2-ethoxyethyl)-2-formylanilino]butyrate (2.4g). To the solution was added potassium tert-butoxide (72mg), the mixture was stirred at 100°C for 1 hour and cooled to room temperature. The reaction solution was added to water, the mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 6/1) to give tert-butyl 7-bromo-1-(2-ethoxyethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.15g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.21 (3H, t, J = 7.0 Hz), 1.53 (9H, s), 2.76 (2H, t, J = 4.4 Hz), 3.26 (2H, t, J = 4.4 Hz), 3.44 - 3.54 (2H, m), 3.52 (2H, q, J = 7.0 Hz), 3.62 - 3.69 (2H, m), 6.82 (1H, d, J = 8.8 Hz), 7.22 (1H, dd, J = 8.8, 2.6 Hz), 7.39 (1H, d, J = 2.2 Hz), 7.46 (1H, s).

## Reference Example 262

In ethyl acetate (22ml) was dissolved tert-butyl 7-bromo-1-(2-ethoxyethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (1.1g). To the solution was added 4N hydrochloric acid/ethyl acetate (11ml) at room temperature, and the mixture was stirred for 24 hours.

An aqueous saturated solution of sodium hydrogen carbonate was added to adjust pH to approximate 4, followed by extraction with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (= 8/1) to give 7-bromo-1-(2-ethoxyethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.73g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.21 (3H, t, J = 7.0 Hz), 2.82 (2H, t, J = 4.4 Hz), 3.30 (2H, t, J = 4.4 Hz), 3.51 (2H, t, J = 4.4 Hz), 3.52 (2H, q, J = 7.0 Hz), 3.67 (2H, t, J = 5.2 Hz), 6.85 (1H, d, J = 8.8 Hz), 7.23 - 7.29 (1H, m), 7.44 (1H, d, J = 2.2 Hz), 7.69 (1H, s).

#### Reference Example 263

In DMF (14.6ml) was dissolved 7-bromo-1-(2-ethoxyethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.73g). To the solution was added thionyl chloride (0.39ml), and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (0.53g) and triethylamine (1.5ml) in THF (15.9ml) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction solution was added

to water, the mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol=3/1) to give 7-bromo-1-(2-ethoxyethyl)-N-[4-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (0.66g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.21 (3H, t, J = 7.0 Hz), 1.63 - 1.82 (4H, m), 2.20 (3H, s), 2.64 (1H, m), 2.87 - 2.96 (4H, m), 3.31 - 3.38 (4H, m), 3.47 - 3.58 (2H, m), 3.56 (2H, s), 3.64 - 3.70 (2H, m), 3.97 - 4.09 (2H, m), 6.85 (1H, d, J = 8.8 Hz), 7.19 - 7.32 (4H, m), 7.40 (1H, d, J = 2.6 Hz), 7.50 - 7.56 (2H, m), 8.01 (1H, s).

Working Example 89 (Production of Compound 89)

In toluene/ethanol/water (= 20/1/1, 14.3ml) was dissolved 7-bromo-1-(2-ethoxyethyl)-N-[4-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (0.32g). To the solution were added 4-(2-propoxyethoxy)phenyl borate (0.16g) and potassium carbonate (0.18g), and the mixture was stirred for 30 minutes under argon atmosphere. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was heated to reflux for 14 hours. After

cooled to room temperature, the reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1). The purified residue was dissolved in ethyl acetate, which was filtered to give a solution. The solvent was removed under reduced pressure, which was recrystallized from isopropyl ether/ethyl acetate to give 1-(2-ethoxyethyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 89) (60mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.2 Hz), 1.59 - 1.80 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 2.92 (2H, m), 3.22 - 3.69 (8H, m), 3.57 (2H, s), 3.69 - 3.73 (2H, m), 3.78 - 3.84 (2H, m), 3.99 - 4.17 (2H, m), 4.16 (2H, t, J = 4.8 Hz), 6.69 (1H, s), 6.95 - 7.03 (3H, m), 7.30 - 7.56 (9H, m).

#### Working Example 90 (Production of Compound 90)

In toluene/ethanol/water (= 20/1/1, 14.3ml) was dissolved 7-bromo-1-(2-ethoxyethyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (0.32g). To the solution were

added 4-(2-butoxyethoxy)phenyl borate (0.17g) and potassium carbonate (0.18g), and the mixture was stirred for 30 minutes under argon atmosphere. To the mixture was added tetrakis(triphenylphosphine)palladium (27mg), and the mixture was heated to reflux for 14 hours. After cooled to room temperature, the reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1). The purified residue was dissolved in ethyl acetate, which was filtered to give a solution. The solvent was removed under reduced pressure, which was recrystallized from isopropyl ether/ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2-ethoxyethyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 90) (15mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.23 (3H, t, J = 7.0 Hz), 1.29 - 1.45 (2H, m), 1.54 - 1.75 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 2.92 (2H, m), 3.30 - 3.44 (4H, m), 3.50 - 3.60 (4H, m), 3.57 (2H, s), 3.67 - 3.72 (2H, m), 3.98 - 4.07 (2H, m), 4.13 - 4.18 (2H, t, J = 4.8 Hz), 6.70 (1H, s), 6.95 - 7.03 (3H, m), 7.27 - 7.55 (9H, m).

## Reference Example 264

In THF (400ml) was dissolved 2-methoxyethanol (20g). To the solution were added triethylamine (47.6ml), 4-dimethylaminopyridine (9.66g) and p-toluenesulfonyl chloride (60.2g), and the mixture was stirred at room temperature for 2 hours. The mixture was stirred at 60°C for 3 hours, the reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, the resulting residue was added dropwise to a solution of 4-[(benzyloxycarbonyl)amino]butyric acid (30.2g) and 60% sodium hydride (10.2g) in THF (453ml). The mixture was stirred at 65°C for 24 hours and cooled to room temperature. The reaction solution was added to water, followed by addition of 1N sodium hydroxide (50ml) and washing with ethyl acetate. The mixture was neutralized with 1N hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated sodium thiosulfate solution and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was dissolved in methylene chloride (90ml), which was added dropwise to a solution of concentrated sulfuric acid (5.4ml) and magnesium sulfate (48.9g) in methylene chloride (450ml). To the

10018324-121201  
mixture was added 2-methyl-2-propanol (48.6ml), and the mixture was stirred at room temperature for 18 hours. An aqueous saturated solution of sodium hydrogen carbonate was added to adjust pH to approximate 8, which was  
5 extracted with ethyl acetate. The extract was washed with water and saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 6/1 → 5/1)  
10 to give tert-butyl 4-[(benzyloxycarbonyl)(2-methoxyethyl)amino]butyrate (10.7g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.43 (9H, s), 1.75 - 1.87 (2H, m), 2.27 (2H, t, J = 7.2 Hz), 3.18 - 3.58 (9H, m), 5.13 (2H, s).

#### Reference Example 265

15 In methanol (300ml) was dissolved tert-butyl 4-[(benzyloxycarbonyl)(2-methoxyethyl)amino]butyrate (30.0g). To the solution was added 10% palladium/carbon (3.0g), and the mixture was stirred for 3 hours under hydrogen atmosphere. 10% palladium/carbon was removed by  
20 filtration with Celite, the solvent was removed under reduced pressure, and the resulting residue was added dropwise to a solution of 5-bromo-2-fluorobenzaldehyde (15.8g) and sodium carbonate (9.9g) in DMF (186ml). The mixture was stirred at 90°C for 65 hours. After cooled  
25 to room temperature, the reaction solution was added to



water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 4/1) to give tert-butyl 4-[4-bromo(2-methoxyethyl)-2-formylanilino]butyrate (6.0g). Tert-butyl 4-[4-bromo(2-methoxyethyl)-2-formylanilino]butyrate (6.0g) was dissolved in toluene (60ml)/2-methyl-2-propanol (6.0ml). To the solution was added potassium tert-butoxide (1.85g), and the mixture was stirred at 100°C for 1 hour. After cooled to room temperature, the reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate=5/1) to give tert-butyl 7-bromo-1-(2-methoxyethyl)-2,3-dihydro-1-benzazepinecarboxylate (1.8g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.53 (9H, s), 2.75 (2H, t, J = 4.4 Hz), 3.24 (2H, t, J = 4.8 Hz), 3.39 (3H, s), 3.55 - 3.65 (4H, m), 6.73 (1H, d, J = 9.0 Hz), 7.19 - 7.40 (3H, m), 7.46 (1H, s).

In toluene/ethanol/water (= 10/1/1, 62.4ml) was dissolved tert-butyl 7-bromo-1-(2-methoxyethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (1.8g). To the solution were added 4-(2-butoxyethoxy)phenyl borate (1.68g) and potassium carbonate (1.55g), and the mixture was stirred for 30 minutes under argon atmosphere. To the mixture was added tetrakis(triphenylphosphine)palladium (0.22g), and the mixture was heated to reflux for 16 hours. After cooled to room temperature, the reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 5/1) to give tert-butyl 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methoxyethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (1.4g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.33 - 1.45 (2H, m), 1.54 (9H, s), 1.53 - 1.65 (2H, m), 2.75 - 2.80 (2H, m), 3.32 (2H, m), 3.41 (3H, s), 3.49 - 3.58 (4H, m), 3.63 - 3.67 (2H, m), 3.72 - 3.83 (2H, m), 4.13 - 4.18 (2H, m), 6.78 (1H, d, J = 5.4 Hz), 6.87 (2H, d, J = 8.8 Hz), 7.38 (1H, dd, J = 8.4, 2.2 Hz), 7.43 - 7.48 (3H, m), 7.65 (1H, s).

## Reference Example 267

In ethyl acetate (28ml) was dissolved tert-butyl 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methoxyethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (1.4g). To the solution was added 4N hydrochloric acid/ethyl acetate (14ml) at room temperature, and the mixture was stirred at 60°C for 2 hours. After cooled to room temperature, an aqueous saturated solution of sodium hydrogen carbonate was added to adjust pH to approximate 5. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (= 6/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2-ethoxyethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.61g, 49%).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.33 - 1.45 (2H, m), 1.54 - 1.66 (2H, m), 2.84 (2H, m), 3.34 - 3.44 (2H, m), 3.41 (3H, s), 3.56 (2H, t, J = 6.6 Hz), 3.52 - 3.59 (2H, m), 3.65 - 3.71 (2H, m), 4.13 - 4.18 (2H, m), 6.98 (2H, d, J = 8.4 Hz), 7.00 (1H, d, J = 8.8 Hz), 7.40 - 7.50 (4H, m), 7.89 (1H, s).

## Working Example 91 (Production of Compound 91)

In THF (12.0ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methoxyethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.60g). To the solution was added oxalyl chloride (0.24ml), and the mixture was

10018321-123001

stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (0.33g) and triethylamine (0.95ml) in THF (9.9ml) under ice-cooling, and the mixture was stirred at room temperature for 14 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 4/1), which was recrystallized from hexane/ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methoxyethyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 91) (0.57g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.30 - 1.45 (2H, m), 1.54 - 1.76 (2H, m), 2.20 (3H, s), 2.64 (1H, m), 2.91 (2H, m), 3.30 - 3.41 (2H, m), 3.41 (3H, s), 3.51 - 3.59 (2H, m), 3.56 (2H, s), 3.65 - 3.71 (2H, m), 3.77 - 3.83 (2H, m), 4.00 - 4.17 (2H, m), 4.15 (2H, t, J = 4.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.30 (1H, d, J = 8.8 Hz), 7.39 - 7.56 (9H, m).

IR (KBr) 3321, 2922, 1640, 1609, 1501, 1244, 1140, 822 cm<sup>-1</sup>.

## Reference Example 268

In THF (12.0ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylate (0.60g). To the solution were added pyridine (0.37ml) and 4-dimethylaminopyridine (56mg), followed by addition of crotonic anhydride (0.58ml). The mixture was stirred at 50°C for 24 hours, and cooled to room temperature. The reaction solution was added to water and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane ethyl acetate = 3/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-[(E)-2-butenoyl]-2,3-dihydro-1-benzazepine-4-carboxylate (0.53g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.0 Hz), 1.34 - 1.46 (2H, m), 1.55 - 1.66 (2H, m), 3.52 - 3.60 (2H, t, J = 6.2 Hz), 3.79 - 3.85 (2H, m), 3.83 (3H, s), 4.15 - 4.21 (2H, m), 4.94 - 5.11 (1H, m), 5.88 - 6.04 (1H, m), 7.02 (2H, d, J = 8.8 Hz), 7.24 - 7.29 (1H, m), 7.53 (3H, d, J = 8.4 Hz), 7.66 (1H, s), 7.74 (1H, s).

## Reference Example 269

In THF (10.6ml)/methanol (10.6ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-[(E)-2-butenoyl]-

2,3-dihydro-1-benzazepine-4-carboxylate (0.53g). To the solution was added 1N sodium hydroxide (5.3ml), and the mixture was stirred at room temperature for 20 hours. pH was adjusted to approximate 5 with 1N hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (= 8/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-[(E)-2-butenoyl]-2,3-dihydro-1-benzazepine-4-carboxylate (0.40g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.97 (3H, t, J = 6.8 Hz), 1.31 - 1.50 (2H, m), 1.54 - 1.63 (2H, m), 1.80 (3H, d, J = 6.4 Hz), 3.57 (2H, t, J = 6.6 Hz), 3.82 (2H, m), 4.19 (2H, m), 4.90 (1H, m), 6.01 (1H, m), 7.03 (2H, d, J = 8.4 Hz), 7.21 (1H, d, J = 8.4 Hz), 7.52 - 7.57 (3H, m), 7.67 (1H, s), 7.84 (1H, s).

Working Example 92 (Production of Compound 92)

In THF (7.8ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-[(E)-2-butenoyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.39g). To the solution were added DMF (two droplets) and oxalyl chloride (0.15ml), and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced

pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (210mg) and triethylamine (0.60ml) in THF (6.3ml) under ice-cooling, and the mixture was stirred at room temperature for 14 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol=4/1), which was recrystallized from isopropyl ether/ethyl acetate to give 1-[(E)-2-butenoyl]-7-[4-(2-butoxyethoxy)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 92) (168mg).

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.94 (3H, t,  $J = 7.2$  Hz), 1.25 - 1.49 (2H, m), 1.54 - 1.82 (9H, m), 2.21 (3H, s), 2.65 (1H, m), 2.93 (3H, s), 3.16 - 3.43 (3H, m), 3.52 - 3.60 (2H, m), 3.56 (2H, s), 3.79 - 3.85 (2H, m), 3.98 - 4.09 (2H, m), 4.91 (1H, m), 6.00 - 6.09 (1H, m), 7.03 (2H, d,  $J = 8.8$  Hz), 7.18 - 7.33 (3H, m), 7.39 - 7.67 (8H, m).

IR (KBr) 2936, 2851, 1659, 1609, 1495, 1250, 1140, 826  $\text{cm}^{-1}$ .

Anal. Calcd.  $\text{C}_{40}\text{H}_{49}\text{N}_3\text{O}_5 \cdot 0.7\text{H}_2\text{O}$  Calcd. C, 72.51; H, 6.32; N, 7.65. Found C, 72.33; H, 6.05; N, 7.42.

## Reference Example 270

4N sodium hydroxide (36ml) was added to 1-isopropyl-2-pyrrolidone (9.2g), and the mixture was stirred for 3.5 hours. After cooled to 0°C, the mixture was neutralized with concentrated hydrochloric acid. After sodium carbonate (15.3g) was added thereto, a solution of 5-bromo-2-fluorobenzaldehyde (7.3g) in dimethyl sulfoxide (96ml) was added thereto, and the mixture was heated to reflux for 5 hours. After cooled to room temperature, pH was adjusted to approximate 4 with 6N hydrochloric acid, and the mixture was extracted with ethyl acetate/THF. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 4/1 → 3/2) to give 4-(4-bromo-2-formylisopropylanilino)butyric acid (0.92g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.12 (6H, d, J = 6.6 Hz), 1.74 (2H, m), 2.37 (2H, t, J = 7.0 Hz), 3.16 (2H, t, J = 6.6 Hz), 3.30 (1H, m), 7.12 (1H, d, J = 8.8 Hz), 7.60 (1H, d, J = 8.8, 2.4 Hz), 7.95 (1H, d, J = 2.4 Hz), 10.21 (1H, s).

## Reference Example 271

In DMF (4.5ml) was dissolved 4-(4-bromo-2-formylisopropylanilino)butyric acid (0.9g). To the solution was added potassium carbonate (0.49g), followed



10016321.121201  
by addition of methyl iodide (0.2ml) and stirring at room temperature 1 hour. To the mixture was added dimethyl carbonate (9ml), followed by addition of a 28% sodium methoxide/methanol solution (1.27g) and stirring at 50°C for 1 hour. After cooled to room temperature, the mixture was neutralized with 2N hydrochloric acid, and extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 20/1 → 8/1) to give methyl 7-bromo-1-isopropyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.50g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.24 (6H, d, J = 6.6 Hz), 2.73 - 2.79 (2H, m), 3.15 (2H, t, J = 4.8 Hz), 3.80 (3H, s), 3.98 (1H, s), 6.70 (1H, d, J = 9.0 Hz), 7.22 (1H, d, J = 2.6 Hz), 7.42 (1H, d, J = 2.6 Hz), 7.55 (1H, s).

#### Reference Example 272

In toluene/ethanol/water (= 10/1/1, 20.4ml) was dissolved methyl 7-bromo-1-isopropyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.50g). To the solution were added 4-(2-butoxyethoxy)phenyl borate (0.48g) and potassium carbonate (0.47g), and the mixture was stirred for 30 minutes under argon atmosphere. To the mixture was added tetrakis(triphenylphosphine)palladium (0.10g),

and the mixture was heated to reflux for 14 hours. After cooled to room temperature, the reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 20/1 → 8/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-isopropyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.44g). Methyl 7-[4-(2-butoxyethoxy)phenyl]-1-isopropyl-2,3-dihydro-1-benzazepine-4-carboxylate (0.44g) was dissolved in THF (8.8ml)/methanol (8.8ml). To the solution was added 1N sodium hydroxide (4.4ml), and the mixture was stirred at 50°C for 4 hours. After cooled to room temperature, pH was adjusted to approximate 5 with 1N hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate/THF, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (12/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-isopropyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (320mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.28 (6H,

d, J = 6.6 Hz), 1.28 - 1.68 (4H, m), 2.77 - 2.83 (2H, m),  
3.20 - 3.26 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.81 (2H, t,  
J = 4.8 Hz), 4.11 (1H, m), 4.13 - 4.18 (2H, m), 6.90 (1H, d,  
J = 8.8 Hz), 6.98 (2H, d, J = 8.4 Hz), 7.25 - 7.54 (4H, m),  
5 7.87 (1H, s).

Working Example 93 (Production of Compound 93)

In THF (6.4ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-isopropyl-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.32g), followed by  
10 addition of DMF (two droplets). To the mixture was added oxalyl chloride (165 $\mu$ l), and the mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-  
15 [methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (183mg) and triethylamine (0.63ml) in THF (5.5ml) under ice-cooling, and the mixture was stirred at room temperature for 3 hours. The reaction solution was added to water, and the mixture was extracted with ethyl  
20 acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 4/1) to give 7-[4-(2-  
25 butoxyethoxy)phenyl]-1-isopropyl-N-[4-[N-methyl-N-

10018321.121201

(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 93) (284mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.0 Hz), 1.29 (6H, d, J = 6.6 Hz), 1.32 - 1.54 (2H, m), 1.57 - 1.76 (6H, m),  
 5 2.20 (3H, s), 2.64 (1H, s), 2.89 (2H, m), 3.24 - 3.43 (4H, m), 3.55 (2H, t, J = 6.2 Hz), 3.56 (2H, s), 3.80 (2H, m), 4.00 - 4.08 (2H, m), 4.10 (1H, m), 4.16 (2H, m), 6.92 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.29 (2H, d, J = 8.8 Hz), 7.40 - 7.56 (8H, m).

10 IR (KBr) 2959, 2870, 1667, 1597, 1514, 1497, 1404, 1242, 820 cm<sup>-1</sup>.

Anal. Calcd. C<sub>39</sub>H<sub>51</sub>N<sub>3</sub>O<sub>4</sub> · 0.5H<sub>2</sub>O Calcd. C, 73.78; N, 6.62; H, 8.26. Found C, 74.04; N, 6.53; H, 8.41.

#### Reference Example 273

15 In THF (27.4ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylate (1.37g). To the solution was added 60% sodium hydride (0.27g) at 0°C, and the mixture was stirred at room temperature for 1 hour. To the mixture  
 20 was added 3-bromo-1-(trimethylsilyl)-1-propyne (1.48ml), and the mixture was stirred at 65°C for 90 hours. After cooled to room temperature, the reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and  
 25 dried with magnesium sulfate. The solvent was removed

under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 3/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(3-trimethylsilyl-2-propynyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.78g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.18 (9H, s), 0.93 (3H, t, J = 7.4 Hz), 1.34 - 1.44 (2H, m), 1.55 - 1.64 (2H, m), 2.82 - 2.90 (2H, m), 3.33 - 3.40 (4H, m), 3.56 (2H, t, J = 6.2 Hz), 3.78 - 3.84 (2H, m), 3.82 (3H, s), 4.07 (2H, s), 4.10 - 4.19 (2H, m), 6.97 - 7.06 (3H, m), 7.43 (4H, m), 7.76 (1H, s).

#### Reference Example 274

In THF (7.8ml)/methanol (7.8ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(3-trimethylsilyl-2-propynyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.78g). To the solution was added 2N potassium hydroxide (7.8ml), and the mixture was stirred at room temperature for 16 hours. pH was adjusted to approximate 4 with 6N hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure and the resulting residue was washed with hexane/ethyl acetate (= 8/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-

(2-propynyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid  
(0.52g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.4 Hz), 1.34 -  
1.47 (2H, m), 1.55 - 1.68 (2H, m), 2.31 (1H, m), 2.84 -  
5 2.95 (2H, m), 3.37 - 3.43 (2H, m), 3.56 (2H, t, J = 6.6 Hz),  
3.78 - 3.84 (2H, m), 4.08 (2H, d, J = 2.2 Hz), 4.14 - 4.19  
(2H, m), 6.99 (2H, d, J = 8.8 Hz), 7.06 (1H, d, J = 8.8 Hz),  
7.45 - 7.56 (4H, m), 7.87 (1H, s).

Reference Example 94 (Production of Compound 94)

10 In THF (10.4ml) was dissolved 7-[4-(2-  
butoxyethoxy)phenyl]-1-(2-propynyl)-2,3-dihydro-1-  
benzazepine-4-carboxylic acid (0.52g). To the solution  
was added DMF (two droplets), followed by addition of  
oxalyl chloride (0.27ml) and stirring at room temperature  
15 for 2 hours. The solvent was removed under reduced  
pressure, a solution of the resulting residue in THF was  
added dropwise to a solution of 4-  
[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline  
(0.30g) and triethylamine (1.04ml) in THF (9.0ml) under  
20 ice-cooling, and the mixture was stirred at room  
temperature for 15 hours. The reaction solution was  
added to water, and the mixture was extracted with ethyl  
acetate. The extract was washed with saturated brine and  
dried with magnesium sulfate. The solvent was removed  
25 under reduced pressure, and the resulting residue was

purified with silica gel column chromatography (ethyl acetate/ethanol = 4/1), which was recrystallized from ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1-(2-propynyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 94) (570mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.0 Hz), 1.33 - 1.46 (2H, m), 1.54 - 1.75 (6H, m), 2.20 (3H, s), 2.32 (1H, m), 2.64 (1H, m), 2.90 - 2.97 (2H, m), 3.30 - 3.42 (6H, m), 3.51 - 3.59 (2H, m), 3.55 (2H, s), 3.77 - 3.83 (2H, m), 4.00 - 4.17 (4H, m), 4.06 (1H, m), 6.97 (2H, d, J = 8.8 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.31 - 7.56 (8H, m), 7.67 (1H, s). IR (KBr) 3322, 3249, 2948, 1642, 1607, 1499, 1240, 1140, 810 cm<sup>-1</sup>.

Anal. Calcd. C<sub>39</sub>H<sub>47</sub>N<sub>3</sub>O<sub>4</sub> Calcd. C, 75.33; N, 6.76; H, 7.62. Found C, 75.39; N, 6.74; H, 7.53.

#### Reference Example 275

In THF (24.0ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylate (1.20g). To the solution was added 60% sodium hydride (0.24g), and the mixture was stirred at room temperature for 1 hour. To the mixture was added 1-bromo-2-butyne (0.80ml), and the mixture was stirred at 65°C for 4 days. After cooled to room temperature, the reaction solution was added to water, and the mixture was

extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 4/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(2-butynyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.50g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.4 Hz), 1.30 - 1.45 (2H, m), 1.53 - 1.68 (2H, m), 1.83 - 1.86 (3H, m), 2.83 - 2.89 (2H, m), 3.30 - 3.38 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.78 - 3.84 (2H, m), 3.81 (3H, s), 4.01 (2H, d, J = 2.2 Hz), 4.13 - 4.18 (2H, m), 6.98 (2H, d, J = 8.8 Hz), 7.04 (1H, d, J = 8.8 Hz), 7.42 - 7.54 (4H, m), 7.76 (1H, s).

#### Reference Example 276

In THF (5.0ml)/methanol (5.0ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(2-butynyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.50g). To the solution was added 2N potassium hydroxide (5.0ml), and the mixture was stirred at 50°C for 3 hours. pH was adjusted to approximate 4 with 6N hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed



with hexane/ethyl acetate (= 8/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2-butyrynyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.40g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.0 Hz), 1.35 - 1.45 (2H, m), 1.55 - 1.64 (2H, m), 1.86 (3H, s), 2.88 (2H, m), 3.38 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.78 - 3.84 (2H, m), 4.02 (2H, d, J = 2.0 Hz), 4.17 (2H, t, J = 4.8 Hz), 6.98 (2H, d, J = 8.6 Hz), 7.05 (1H, d, J = 8.4 Hz), 7.44 - 7.55 (4H, m), 7.87 (1H, s).

IR (KBr) 2922, 1677, 1607, 1503, 1275, 1248, 1192, 924, 806 cm<sup>-1</sup>.

Working Example 95 (Production of Compound 95)

In THF (8.0ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(2-butyrynyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.40g). To the solution was added DMF (two droplets), followed by addition of oxalyl chloride (0.20ml) and stirring at room temperature for 1 hour. The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (224mg) and triethylamine (0.64ml) in THF (6.7ml) under ice-cooling, and the mixture was stirred at room temperature for 12 hours. The reaction solution was added to water, and the mixture was extracted with ethyl

acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol= 4/1 → 3/1), which was recrystallized from hexane/ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2-butyryl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 95) (359mg).

m.p 129 - 131°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.0 Hz), 1.26 - 1.48 (2H, m), 1.54 - 1.76 (6H, m), 1.86 (23H, s), 2.21 (3H, s), 2.64 (1H, m), 2.96 (2H, m), 3.30 - 3.44 (4H, m), 3.55 (2H, t, J = 6.2 Hz), 3.56 (2H, s), 3.80 (2H, t, J = 4.8 Hz), 4.00 - 4.10 (4H, m), 4.13 - 4.18 (2H, m), 6.98 (2H, d, J = 8.8 Hz), 7.07 (2H, d, J = 8.8 Hz), 7.30 (2H, m), 7.39 - 7.58 (8H, m).

IR (KBr) 2953, 1655, 1605, 1514, 1499, 1244, 1138, 814 cm<sup>-1</sup>.

Anal. Calcd. C<sub>40</sub>H<sub>49</sub>N<sub>3</sub>O<sub>4</sub> Calcd. C, 75.56; N, 6.61; H, 7.77.

Found C, 75.53; N, 6.52; H, 7.79.

#### Reference Example 277

In THF (11.2ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylate (0.56g). To the solution were added pyridine (0.17ml) and ethyl chloroformate (0.18ml), and the

10018324.124204

mixture was stirred at room temperature for 3 hours. To the mixture was added 4-dimethylaminopyridine (169mg), and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 3/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(ethoxycarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylate (580mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.0 Hz), 1.26 - 1.42 (5H, m), 1.55 - 1.62 (2H, m), 2.93 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.66 - 3.84 (4H, m), 3.83 (3H, s), 4.14 - 4.29 (4H, m), 7.00 (2H, d, J = 8.8 Hz), 7.47 - 7.59 (5H, m), 7.73 (1H, s).

#### Reference Example 278

In THF (8.7ml)/methanol (8.7ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(ethoxycarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.58g). To the solution was added 1N sodium hydroxide (8.7ml), and the mixture was stirred at 50°C for 4 hours. pH was adjusted to approximate 4 with 6N hydrochloric acid, and the solvent was concentrated to half under reduced pressure.

10018331-121204  
T02T2T T22BT001

The concentrated material was extracted with ethyl acetate, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (= 8/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(ethoxycarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.46g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.0 Hz), 1.29 (3H, t, J = 6.6 Hz), 1.56 - 1.66 (2H, m), 2.95 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.75 - 3.85 (4H, m), 4.17 (2H, t, J = 4.8 Hz), 4.23 (2H, q, J = 6.6 Hz), 7.01 (2H, d, J = 8.4 Hz), 7.51 - 7.62 (5H, m), 7.84 (1H, s).

Working Example 96 (Production of Compound 96)

In THF (9.2ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(ethoxycarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.46g). To the solution was added DMF (two droplets), followed by addition of oxalyl chloride (0.22ml) and stirring at room temperature for 1 hour. The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (246mg) and triethylamine (0.71ml) in THF (7.4ml) under ice-cooling, and the mixture was stirred at room temperature for 12 hours. The reaction solution was

added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was

5 purified with silica gel column chromatography (ethyl acetate/ethanol = 4/1 → 3/1), which was recrystallized from hexane/ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-1-(ethoxycarbonyl)-4-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-

10 benzazepine-4-carboxamide (Compound 96) (0.48g).

m.p 152 - 154°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.29 (3H, t, J = 6.4 Hz), 1.33 - 1.45 (2H, m), 1.54 - 1.75 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 3.00 (2H, m), 3.30 - 3.43 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.57 (2H, s), 3.81 (2H, m),

15 4.00 - 4.20 (2H, m), 4.17 (2H, t, J = 4.8 Hz), 4.23 (2H, q, J = 6.4 Hz), 7.00 (2H, d, J = 8.8 Hz), 7.31 (2H, d, J = 8.8 Hz), 7.46 - 7.60 (8H, m).

IR (KBr) 3308, 2955, 2870, 1699, 1609, 1497, 1250, 1208,

20 1140, 922, 826, 731 cm<sup>-1</sup>.

Anal. Calcd. C<sub>38</sub>H<sub>48</sub>N<sub>3</sub>O<sub>6</sub> Calcd. C, 71.00; N, 6.54; H, 7.53.  
Found C, 71.14; N, 6.26; H, 7.36.

#### Reference Example 279

In pyridine (4.3ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-

25

carboxylate (0.43 g). To the solution was added allyl  
chloroformate (0.23ml), and the mixture was stirred at  
room temperature for 14 hours. To the mixture was added  
4-dimethylaminopyridine (40mg), and the mixture was  
5 stirred at room temperature for 2 hours. The reaction  
solution was added to water, and the mixture was  
extracted with ethyl acetate. The extract was washed  
with saturated brine, and dried with magnesium sulfate.  
The solvent was removed under reduced pressure, and the  
10 resulting residue was purified with silica gel column  
chromatography (hexane/ethyl acetate = 3/1) to give  
methyl 1-(allyloxycarbonyl)-7-[4-(2-butoxyethoxy)phenyl]-  
2,3-dihydro-1-benzazepine-4-carboxylate (0.30g).  
<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.0 Hz), 1.28 -  
15 1.45 (2H, m), 1.54 - 1.66 (2H, m), 2.94 (2H, m), 3.56 (2H,  
t, J = 6.6 Hz), 3.78 - 3.85 (4H, m), 3.83 (3H, s), 4.15 -  
4.19 (2H, m), 4.67 (1H, m), 5.24 (1H, m), 5.94 (1H, m),  
7.00 (2H, d, J = 8.8 Hz), 7.43 - 7.60 (5H, m), 7.73 (1H, s).

#### Reference Example 280

20 In THF (4.5ml)/ethanol (4.5ml) was dissolved methyl  
1-(allyloxycarbonyl)-7-[4-(2-butoxyethoxy)phenyl]-2,3-  
dihydro-1-benzazepine-4-carboxylate (0.30g). To the  
solution was added 1N sodium hydroxide (3.0ml), and the  
mixture was stirred at room temperature for 4 hours. pH  
25 was adjusted to approximate 4 with 1N hydrochloric acid,

and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate, the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (= 8/1) to give 1-(allyloxycarbonyl)-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.25g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.2 Hz), 1.30 - 1.49 (2H, m), 1.54 - 1.69 (2H, m), 2.97 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.75 - 3.87 (4H, m), 4.18 (2H, d, J = 4.8 Hz), 4.68 (1H, m), 5.24 (1H, m), 5.96 (1H, m), 7.01 (2H, d, J = 8.4 Hz), 7.49 - 7.61 (5H, m), 7.85 (1H, s).

#### Working Example 97 (Production of Compound 97)

In THF (4.8ml) was dissolved 1-(allyloxycarbonyl)-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.24g). To the solution was added DMF (two droplets), followed by addition of oxalyl chloride (0.11ml) and stirring at room temperature for 1 hour.

The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (125mg) and triethylamine (0.36ml) in THF (5.0ml) under ice-cooling, and the mixture was stirred at room temperature for 12 hours. The reaction

solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 4/1 → 3/1), which was recrystallized from hexane/ethyl acetate to give 1-(allyloxycarbonyl)-7-[4-(2-butoxyethoxy)phenyl]-4-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 97) (0.23g).

mp 160 - 162°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.33 - 1.49 (2H, m), 1.54 - 1.75 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 3.02 (2H, m), 3.37 (2H, td, J = 11.0, 2.8 Hz), 3.56 (2H, t, J = 6.6 Hz), 3.57 (2H, s), 3.81 (2H, m), 3.99 - 4.08 (2H, m), 3.99 - 4.08 (2H, m), 4.14 - 4.20 (2H, m), 4.67 (1H, m), 5.25 (1H, m), 5.92 (1H, m), 7.00 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.47 - 7.58 (9H, m).

IR (KBr) 3353, 2953, 2845, 1686, 1658, 1611, 1533, 1316, 1206, 1086, 922, 829, 764 cm<sup>-1</sup>.

Anal. Calcd. C<sub>40</sub>H<sub>49</sub>N<sub>3</sub>O<sub>6</sub> Calcd. C, 71.94; N, 6.29; H, 7.40. Found C, 71.69; N, 6.33; H, 7.49.

#### Reference Example 281

In 1,2-dichloroethane (15ml) was dissolved methyl 7-



[4-(2-butoxyethoxy)phenyl]-1-benzazepine-4-carboxylate (0.50g). To the solution were added 1,3-thiazole-5-carbaldehyde (0.43g) and sodium triacetoxymethylborohydride (0.80g), and the mixture was stirred at room temperature for 24 hours. To the mixture was added sodium triacetoxymethylborohydride (0.27g), and the mixture was stirred for 6 hours. The solvent was removed under reduced pressure, the resulting residue was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate= 3/2 → 2/3) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(1,3-thiazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.50g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.34 - 1.44 (2H, m), 1.54 - 1.65 (2H, m), 2.79 (2H, m), 3.30 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.78 - 3.83 (2H, m), 3.81 (3H, s), 4.16 (2H, m), 6.94 - 7.10 (3H, m), 7.39 - 7.57 (3H, m), 7.56 (1H, d, J = 2.2 Hz), 7.79 (1H, s), 7.83 (1H, s), 8.78 (1H, s).

#### Reference Example 282

In THF (5.0ml)/methanol (10ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(1,3-thiazol-5-ylmethyl)-

2,3-dihydro-1-benzazepine-4-carboxylate (0.50g). To the solution was added 1N sodium hydroxide solution (5.0ml), and the mixture was stirred at room temperature for 16 hours. pH was adjusted to approximate 5 with 1N

5 hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate/THF, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure,  
10 and the resulting residue was washed with hexane ethyl acetate (8/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(1,3-thiazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (385mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.4 Hz), 1.34 -  
15 1.44 (2H, m), 1.55 - 1.67 (2H, m), 2.82 (2H, m), 3.33 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 4.8 Hz), 4.17 (2H, m), 4.77 (2H, s), 6.97 (1H, d, J = 8.8 Hz), 6.99 (2H, d, J = 8.8 Hz), 7.41 - 7.50 (3H, m), 7.58 (1H, d, J = 1.8 Hz), 7.85 (1H, s), 7.91 (1H, s), 8.81 (1H, s).

20 Working Example 98 (Production of Compound 98)

In methylene chloride (19ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(1,3-thiazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.38g). To the solution was added DMF (two droplets), followed by  
25 addition of oxalyl chloride (90μl) and stirring at room

temperature for 2 hours to give a solution, which was added dropwise to a solution of 4-

[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (198mg) and triethylamine (2.75ml) in methylene chloride

5 (7.6ml), and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with methylene chloride.

The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under

10 reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 2/1) to give 7-[4-(2-

butoxyethoxy)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1-(1,3-thiazol-5-ylmethyl)-2,3-

15 dihydro-1-benzazepine-4-carboxamide (Compound 98) (190mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.30 - 1.48 (2H, m), 1.53 - 1.72 (2H, m), 2.21 (3H, s), 2.66 (1H, m), 2.87 (2H, m), 3.30 - 3.43 (4H, m), 3.55 (2H, t, J = 6.6 Hz), 3.57 (2H, s), 3.80 (2H, m), 3.97 - 4.09 (2H, m), 4.16  
20 (2H, m), 4.77 (2H, m), 6.98 (4H, d, J = 8.8 Hz), 7.27 - 7.58 (9H, m), 7.84 (1H, s), 8.79 (1H, s).

IR (KBr) 3293, 2955, 1645, 1609, 1518, 1499, 1406, 1242, 1140, 821 cm<sup>-1</sup>.

#### Reference Example 283

25 In ethanol (50ml) was dissolved acetyl thioamide

10018321-121201

(5.0g). To the solution was added ethyl 2-chloroacetoacetate (11.0g), and the mixture was heated to reflux for 16 hours. After cooled to room temperature, the solvent was removed under reduced pressure, the resulting residue was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 1/1) to give ethyl 2,3-dimethyl-1,3-thiazole-5-carboxylate (9.1g).

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.36 (3H, t,  $J = 7.2$  Hz), 2.68 (3H, m), 2.69 (3H, s), 4.32 (2H, q,  $J = 7.2$  Hz).

#### Reference Example 284

A solution of ethyl 2,4-dimethyl-1,3-thiazole-5-carboxylate (5.0g) in THF (50ml) was added dropwise to a solution of aluminum lithium hydride (1.1g) in THF (150ml) under ice-cooling. After stirred at room temperature for 4 hours, water (1.1ml), 15% sodium hydroxide solution (1.1ml) and water (3.3ml) were added thereto, and the mixture was stirred for 10 minutes. The mixture was filtered with Celite, and washed with methanol. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 1/2) to

give (2,4-dimethyl-1,3-thiazol-5-yl)methanol (2.0g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.31 (3H, s), 2.62 (3H, s), 3.14 (1H, br), 4.72 (2H, d, J = 5.0 Hz).

#### Reference Example 285

5 In THF (20ml) was dissolved (2,4-dimethyl-1,3-thiazol-5-yl)methanol (1.0g). To the solution was added active manganese dioxide (6.0g), and the mixture was stirred at room temperature for 3 hours. To the mixture was added active manganese dioxide (3.0g), and the  
10 mixture was stirred at room temperature for 1 hour. The mixture was filtered with Celite and washed with methanol. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate/methanol = 10/10/1)  
15 to give 2,4-dimethyl-1,3-thiazole-5-carbaldehyde (0.32g).  
<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.70 (3H, s), 2.73 (3H, s), 10.13 (1H, s).

#### Reference Example 286

In 1,2-dichloroethane (21ml) was dissolved methyl 7-  
20 [4-(2-butoxyethoxy)phenyl]-1-benzazepine-4-carboxylate (0.70g). To the solution were added 2,4-dimethyl-1,3-thiazole-5-carbaldehyde (0.62g) and sodium triacetoxymethylborohydride (1.5g), and the mixture was stirred at room temperature for 36 hours. After stirred at 60°C  
25 for 12 hours, the mixture was cooled to room temperature,

and the solvent was removed under reduced pressure. The residue was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate = 1/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(2,4-dimethyl-1,3-thiazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.26g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.37 - 1.44 (2H, m), 1.54 - 1.67 (2H, m), 2.40 (3H, s), 2.62 (3H, s), 2.76 (2H, t, J = 4.4 Hz), 3.24 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.78 - 3.83 (2H, m), 3.81 (3H, s), 4.16 (2H, m), 4.56 (2H, s), 6.93 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.39 - 7.49 (3H, m), 7.55 (1H, d, J = 2.2 Hz), 7.78 (1H, s).

#### Reference Example 287

In THF (5.0ml)/methanol (2.5ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(2,4-dimethyl-1,3-thiazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.25g). To the solution was added 1N sodium hydroxide solution (2.5ml), and the mixture was stirred at room temperature for 16 hours. pH was adjusted to approximate 5 with 1N hydrochloric acid, and the solvent was

concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate/THF, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (8/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2,4-dimethyl-1,3-thiazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (190mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.32 - 1.46 (2H, m), 1.56 - 1.68 (2H, m), 2.42 (3H, s), 2.64 (3H, s), 2.78 (2H, m), 3.27 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 4.8 Hz), 4.17 (2H, t, J = 4.8 Hz), 4.59 (2H, s), 6.92 - 7.10 (3H, m), 7.42 - 7.50 (3H, m), 7.57 (1H, d, J = 1.8 Hz), 7.89 (1H, s).

IR (KBr) 2924, 1684, 1607, 1501, 1235, 1126, 968, 810 cm<sup>-1</sup>.

#### Working Example 99 (Production of Compound 99)

In methylene chloride (9.5ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(2,4-dimethyl-1,3-thiazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.19g). To the solution was added DMF (two droplets), followed by addition of thionyl chloride (32μl) and stirring at room temperature for 2 hours, to give a solution, which was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethylaniline (91mg)

and triethylamine (1.0ml) in methylene chloride (5.6ml), and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with methylene chloride. The

5 extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 2/1), which was recrystallized from hexane/ethyl acetate  
10 to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2,4-dimethyl-1,3-thiazol-5-ylmethyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)amino]methylphenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 99) (135mg).

mp 125 - 128°C.

15 <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.37 - 1.45 (2H, m), 1.57 - 1.77 (6H, m), 2.21 (3H, s), 2.43 (3H, s), 2.64 (3H, s), 2.84 (2H, m), 3.28 - 3.44 (2H, m), 3.52 - 3.59 (2H, m), 3.55 (2H, s), 3.81 (2H, t, J = 4.8 Hz), 3.98 - 4.08 (2H, m), 4.16 (2H, t, J = 4.8 Hz), 4.59 (2H, s),  
20 6.96 (1H, d, J = 8.8 Hz), 6.99 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.40 - 7.56 (8H, m).

IR (KBr) 3227, 2959, 1655, 1603, 1499, 1406, 1315, 1248, 1177, 820 cm<sup>-1</sup>.

Anal. Calcd. C<sub>42</sub>H<sub>52</sub>N<sub>4</sub>O<sub>4</sub> · 0.5H<sub>2</sub>O Calcd. C, 70.26; N, 7.80; H, 7.44. Found C, 70.36; N, 7.47; H, 7.54.

25



## Reference Example 288

To a solution of aluminum lithium hydride (2.5g) in THF (282ml) was added dropwise a solution of ethyl tetrazole-5-carboxylate (9.4g) in THF (94ml) under ice-cooling. The mixture was stirred at room temperature for 3 hours, followed by addition of water (2.5ml), 15% sodium hydroxide solution (2.5ml) and water (7.5ml), and stirring for 10 minutes. The mixture was filtered with Celite and washed with methanol. The solvent was removed under reduced pressure, and the resulting residue was dissolved in DMF (190ml). To the solution was added active manganese dioxide (37g), and the mixture was stirred at room temperature for 16 hours. The mixture was filtered with Celite and washed with methanol. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (=1/1) to give tetrazole-5-carbaldehyde (4.6g).

$^1\text{H-NMR}$  (200 MHz, DMSO- $d_6$ )  $\delta$  10.10 (1H, s).

## Reference Example 289

In 1,2-dichloroethane (14ml)/acetic acid (7ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1-benzazepine-4-carboxylate (0.70g). To the solution were added tetrazole-5-carbaldehyde (0.31g) and sodium triacetoxyborohydride (1.5g), and the mixture was stirred at 40°C for 18 hours. The mixture was cooled to

Amen.  
 B 55

room temperature, and the solvent was removed under reduced pressure. The resulting residue was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 15/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(tetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.67g)

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.36 - 1.45 (2H, m), 1.55 - 1.66 (2H, m), 2.74 (2H, m), 3.33 (2H, m), 3.59 (2H, t, J = 6.6 Hz), 3.67 (3H, s), 3.83 (2H, t, J = 4.6 Hz), 4.15 (2H, m), 4.85 (2H, s), 6.79 (1H, d, J = 8.6 Hz), 6.88 (2H, d, J = 8.6 Hz), 7.27 - 7.37 (3H, m), 7.45 (1H, d, J = 2.0 Hz), 7.68 (1H, s).

#### Reference Example 290

In THF (6.7ml)/methanol (6.7ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(tetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.25g). To the solution was added 1N sodium hydroxide solution (6.7ml), and the mixture was stirred at 50°C for 4 hours. pH was adjusted to approximate 4 with 1N hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with

ethyl acetate/THF, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (2/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(tetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.45g).

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 0.89 (3H, t, J = 7.2 Hz), 1.04 - 1.55 (4H, m), 2.72 (2H, m), 3.33 (2H, m), 3.46 (2H, t, J = 6.6 Hz), 3.72 (3H, s), 4.11 (2H, t, J = 4.6 Hz), 4.91 (2H, s), 6.91 - 7.00 (3H, m), 7.43 - 7.71 (5H, m).

Working Example 100 (Production of Compound 100)

In THF(8.1ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(tetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.27g). To the solution was added DMF (two droplets), followed by addition of thionyl chloride (51μl) and stirring at room temperature for 1 hour, to give a solution, which was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (145mg) and triethylamine (1.62ml) in THF (8.1ml) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate.

The solvent was removed under reduced pressure, and the resulting residue was dissolved in ethanol. To the solution was added ethyl acetate, and the precipitates were collected by filtration, which was recrystallized from hexane/ethanol to give 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1-(tetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 100) (42mg).

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 0.89 (3H, t, J = 7.2 Hz), 1.28 - 1.39 (2H, m), 1.47 - 1.55 (2H, m), 1.55 - 1.92 (4H, m), 2.28 - 2.38 (1H, m), 2.34 (3H, s), 2.83 (2H, m), 3.24 - 3.45 (4H, m), 3.46 (2H, t, J = 6.4 Hz), 3.71 (2H, m), 3.86 - 3.99 (4H, m), 4.11 (2H, m), 4.81 (2H, s), 6.58 (1H, d, J = 8.8 Hz), 6.99 (2H, d, J = 8.8 Hz), 7.11 (2H, d, J = 8.4 Hz), 7.33 - 7.75 (7H, m), 9.89 (1H, s).

#### Reference Example 291

In acetonitrile (100ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(tetrazol-4-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (1.0g). To the solution were added potassium carbonate (0.87g) and methyl iodide (0.31ml), and the mixture was stirred at room temperature for 4 hours. The solvent was concentrated to half under reduced pressure, which was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and

dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (= 8/1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(1-methyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.33g) and methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.44g).

<sup>1</sup>H-NMR (1-methyl compound; 200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.30 - 1.44 (2H, m), 1.45 - 1.66 (2H, m), 2.59 (2H, m), 3.55 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 4.8 Hz), 3.95 (3H, s), 4.16 (2H, t, J = 4.8 Hz), 4.86 (2H, s), 6.96 (1H, d, J = 8.4 Hz), 6.99 (2H, d, J = 8.8 Hz), 7.26 - 7.48 (3H, m), 7.57 (1H, d, J = 2.2 Hz), 7.78 (1H, s).

<sup>1</sup>H-NMR (2-methyl compound; 200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.22 - 1.44 (2H, m), 1.55 - 1.65 (2H, m), 2.86 (2H, m), 3.42 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.77 - 3.83 (2H, m), 3.81 (3H, s), 4.15 (2H, t, J = 4.8 Hz), 4.36 (23H, s), 4.75 (2H, s), 6.97 (2H, d, J = 8.2 Hz), 7.13 (1H, d, J = 8.8 Hz), 7.39 - 7.54 (3H, m), 7.78 (1H, s).

#### Reference Example 292

In THF (6.4ml)/methanol (3.2ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(1-methyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.32g).

To the solution was added 1N sodium hydroxide solution (3.2ml), and the mixture was stirred at room temperature for 14 hours. pH was adjusted to approximate 4 with 1N hydrochloric acid, and the solvent was concentrated to half under reduced pressure. The concentrated material was extracted with ethyl acetate/THF, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl acetate (5/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(1-methyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.25g).

<sup>1</sup>H-NMR (200 MHz, DMSO-d<sub>6</sub>) δ 0.89 (3H, t, J = 7.2 Hz), 1.27 - 1.41 (2H, m), 1.44 - 1.57 (2H, m), 2.69 (2H, m), 3.32 (2H, m), 3.47 (2H, t, J = 6.6 Hz), 3.72 (2H, m), 4.03 (3H, s), 4.09 (2H, m), 4.96 (2H, s), 6.87 - 6.99 (3H, m), 7.43 (1H, d, J = 8.8 Hz), 7.53 - 7.63 (3H, m), 7.71 (1H, s).

IR (KBr) 2957, 2932, 1667, 1609, 1505, 1435, 1273, 1244, 1119, 828, 797 cm<sup>-1</sup>.

Working Example 101 (Production of Compound 101)

In THF(6.9ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(1-methyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (230mg). To the solution was added DMF (two droplets), followed by addition of oxalyl chloride (63ml) and stirring at room

temperature for 1 hour, to give a solution, which was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (120mg) and triethylamine (1.34ml) in THF (6.9ml) under ice-cooling, and the mixture was stirred at room temperature for 3 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1), which was recrystallized from hexane/ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1-(1-methyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 101) (114mg).

mp 132 - 135°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.31 - 1.46 (2H, m), 1.56 - 1.81 (6H, m), 2.20 (3H, s), 2.54 - 2.73 (3H, m), 2.95 (2H, m), 3.30 - 3.42 (4H, m), 3.51 - 3.59 (2H, t, J = 6.2 Hz), 3.56 (2H, s), 3.78 - 3.84 (2H, m), 3.96 - 4.17 (2H, m), 3.98 (3H, s), 4.15 (2H, t, J = 4.8 Hz), 4.81 (2H, s), 6.96 (2H, d, J = 8.4 Hz), 6.98 (1H, d, J = 8.4 Hz), 7.40 - 7.58 (7H, m), 7.70 (1H, s).

IR (KBr) 3294, 2932, 1659, 1607, 1516, 1501, 1406, 1360, 1244, 1138, 820  $\text{cm}^{-1}$ .

Anal. Calcd.  $\text{C}_{39}\text{H}_{49}\text{N}_7\text{O}_4$  Calcd. C, 68.90; N, 14.42; H, 7.26.  
Found C, 68.82; N, 14.14; H, 7.08.

5           Reference Example 293

In THF (4.3ml)/methanol (3.2ml) was dissolved methyl  
7-[4-(2-butoxyethoxy)phenyl]-1-(2-methyltetrazol-5-  
ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.43g).  
To the solution was added 1N sodium hydroxide solution  
10 (4.3ml), and the mixture was stirred at room temperature  
for 14 hours. pH was adjusted to approximate 4 with 1N  
hydrochloric acid, and the solvent was concentrated to  
half under reduced pressure. The concentrated material  
was extracted with ethyl acetate, and the extract was  
15 washed with saturated brine and dried with magnesium  
sulfate. The solvent was removed under reduced pressure,  
and the resulting residue was washed with hexane/ethyl  
acetate (= 5/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-  
(2-methyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-  
20 4-carboxylic acid (0.37g).

$^1\text{H}$ -NMR (200 MHz,  $\text{DMSO-d}_6$ )  $\delta$  0.89 (3H, t,  $J = 7.2$  Hz), 1.27 -  
1.41 (2H, m), 1.43 - 1.58 (2H, m), 2.76 (2H, m), 3.33 (2H,  
m), 3.47 (2H, t,  $J = 6.6$  Hz), 3.69 - 3.74 (2H, m), 4.07 -  
4.12 (2H, m), 4.37 (3H, s), 4.81 (2H, s), 6.97 (2H, d),  
25 7.06 (1H, d,  $J = 8.8$  Hz), 7.42 - 7.60 (4H, m), 7.70 (1H, s).



IR (KBr) 3034, 2934, 1672, 1607, 1501, 1404, 1246, 1190, 1132, 816  $\text{cm}^{-1}$ .

Working Example 102 (Production of Compound 102)

In THF(10.2ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.34mg). To the solution was added DMF (two droplets), followed by addition of oxalyl chloride (93ml) and stirring at room temperature for 1 hour, to give a solution, which was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]aniline (177mg) and triethylamine (1.98ml) in THF(10.2ml) under ice-cooling, and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1), which was recrystallized from hexane/ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-1-(2-methyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 102) (193mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.32 - 1.45 (2H, m), 1.57 - 1.76 (6H, m), 2.21 (3H, s), 2.65 (1H, m), 2.95 (2H, m), 3.30 - 3.48 (4H, m), 3.55 (2H, t, J = 6.6 Hz), 3.57 (2H, s), 3.77 - 3.83 (2H, m), 3.98 - 4.08 (2H, m),  
5 4.10 - 4.18 (2H, m), 4.37 (3H, s), 4.78 (2H, s), 6.97 (2H, d, J = 8.8 Hz), 7.05 (1H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.39 - 7.56 (8H, m).

IR (KBr) 3312, 2930, 1644, 1607, 1503, 1406, 1360, 1242, 1140, 810 cm<sup>-1</sup>.

10 Working Example 103 (Production of Compound 103)

To a solution of 1-(3-methoxypropyl)-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (250mg) in THF (10ml) were added thionyl chloride (0.083ml) and DMF (one droplet) at room  
15 temperature, and the mixture was stirred for 1.5 hours. The solvent was evaporated under reduced pressure, and the resulting residue was dissolved in THF (15ml), which was added dropwise to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (138mg) and  
20 triethylamine (0.48ml) in THF (3ml) at 0°C. The mixture was stirred at room temperature for 3 hours, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and dried with magnesium sulfate. After  
25 concentration under reduced pressure, the residue was

100183221-121201  
T02T2T-T228T00T

purified with column chromatography (ethanol : ethyl acetate 1 : 4 → 1 : 3 → 1 : 2), and the resulting crystals were purified by recrystallization (hexane-ethyl acetate) to give 1-(3-methoxypropyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 103) (264mg) as yellow crystals. mp 87 - 90°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.5 Hz), 1.53 - 1.82 (6H, m), 1.90 - 2.06 (2H, m), 2.21 (3H, s), 2.51 - 2.74 (1H, m), 2.86 - 2.97 (2H, m), 3.28 - 3.66 (15H, m), 3.81 (2H, t, J = 4.9 Hz), 3.98 - 4.11 (2H, m), 4.16 (2H, t, J = 4.9 Hz), 6.95 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.38 - 7.57 (8H, m).

IR (KBr) 3233, 1638, 1607, 1516, 1501, 1314, 1246, 1186, 1117 cm<sup>-1</sup>.

Anal. Calcd. C<sub>39</sub>H<sub>51</sub>N<sub>3</sub>O<sub>5</sub> Calcd. C, 72.98; H, 8.01; N, 6.55. Found C, 72.65; H, 7.98; N, 6.35.

#### Working Example 104 (Production of Compound 104)

To a solution of 7-[4-(2-butoxyethoxy)phenyl]-1-(3-methoxypropyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (200mg) in THF (10ml) were added thionyl chloride (0.064ml) and DMF (one droplet) at room temperature, and the mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure, and the resulting

residue was dissolved in THF (15ml), which was added dropwise to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (107mg) and triethylamine (0.37ml) in THF (5ml) at 0°C. The mixture was stirred at room temperature for 18 hours, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried with magnesium sulfate. After concentration under reduced pressure, the residue was purified with column chromatography (ethanol : ethyl acetate = 1 : 3), and the resulting crystals were purified by recrystallization (hexane-ethyl acetate) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(3-methoxypropyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 104) (264.2mg) as yellow crystals. mp 87 - 90°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.3 Hz), 1.32 - 1.46 (2H, m), 1.50 - 1.82 (6H, m), 1.89 - 2.03 (2H, m), 2.21 (3H, s), 2.55 - 2.72 (1H, m), 2.84 - 2.96 (2H, m), 3.28 - 3.61 (15H, m), 3.80 (2H, t, J = 4.8 Hz), 3.98 - 4.09 (2H, m), 4.16 (2H, t, J = 4.8 Hz), 6.95 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.31 (2H, d, J = 8.4 Hz), 7.36 - 7.57 (8H, m).

IR (KBr) 3334, 1640, 1609, 1516, 1503, 1314, 1244, 1184,

10018321.121201

1119  $\text{cm}^{-1}$ .

Anal. Calcd.  $\text{C}_{40}\text{H}_{53}\text{N}_3\text{O}_5 \cdot 0.5\text{H}_2\text{O}$  Calcd. C, 72.26; H, 8.18; N, 6.32. Found C, 72.51; H, 7.93; N, 6.10.

Working Example 105 (Production of Compound 105)

- 5 To a solution of 1-(3-ethoxypropyl)-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (250mg) in THF (10ml) were added thionyl chloride (0.080ml) and DMF (one droplet) at room temperature, and the mixture was stirred for 1.5 hours.
- 10 The solvent was evaporated under reduced pressure, and the resulting residue was dissolved in THF (20ml), which was added dropwise to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (133mg) and triethylamine (0.46ml) in THF (3ml) at 0°C. The mixture
- 15 was stirred at room temperature for 2.5 hours, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, and dried with magnesium sulfate. After concentration under reduced pressure, the residue was
- 20 purified with column chromatography (ethanol : ethyl acetate = 1 : 9  $\rightarrow$  1 : 3), and the resulting crystals were purified by recrystallization (hexane-ethyl acetate) to give 1-(3-ethoxypropyl)-N-[4-[[N-methyl-N-
- 25 tetrahydropyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-

carboxamide (Compound 105) (242mg) as yellow crystals.

mp 99 - 101°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.5 Hz), 1.23 (3H, t, J = 6.9 Hz), 1.53 - 1.82 (6H, m), 1.90 - 2.04 (2H, m),  
5 2.21 (3H, s), 2.53 - 2.73 (1H, m), 2.87 - 2.96 (2H, m),  
3.30 - 3.60 (14H, m), 3.81 (2H, t, J = 5.0 Hz), 3.98 - 4.10  
(2H, m), 4.17 (2H, t, J = 5.0 Hz), 6.95 - 7.00 (3H, m),  
7.30 (2H, d, J = 8.4 Hz), 7.36 - 7.58 (8H, m).

IR (KBr) 3305, 1640, 1607, 1501, 1406, 1314, 1244, 1123 cm<sup>-1</sup>.

10 Anal. Calcd. C<sub>40</sub>H<sub>53</sub>N<sub>3</sub>O<sub>5</sub> · 0.25H<sub>2</sub>O Calcd. C, 72.75; H, 8.18; N, 6.36. Found C, 72.81; H, 8.08; N, 6.27.

Working Example 106 (Production of Compound 106)

To a solution of 7-[4-(2-butoxyethoxy)phenyl]-1-(3-ethoxypropyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic  
15 acid (250mg) in THF (10ml) were added thionyl chloride  
(0.078ml) and DMF (one droplet) at room temperature, and  
the mixture was stirred for 1.5 hours. The solvent was  
evaporated under reduced pressure, and the resulting  
20 residue was dissolved in THF (20ml), which was added  
dropwise to a solution of 4-[[N-methyl-N-  
(tetrahydropyran-4-yl)amino]methyl]aniline (128mg) and  
triethylamine (0.44ml) in THF (3ml) at 0°C. The mixture  
was stirred at room temperature for 64 hours, water was  
25 added thereto, and the mixture was extracted with ethyl

acetate. The organic layer was washed with saturated brine, and dried with magnesium sulfate. After concentration under reduced pressure, the residue was purified with column chromatography (ethanol : ethyl acetate = 1 : 4), and the resulting crystals were purified by recrystallization (hexane-ethyl acetate) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(3-ethoxypropyl)-N-[4-[[N-methyl-N-tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 106) (224mg) as yellow crystals. mp 95 - 97°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.3 Hz), 1.24 (3H, t, J = 6.9 Hz), 1.30 - 1.48 (2H, m), 1.52 - 1.84 (6H, m), 1.90 - 2.06 (2H, m), 2.21 (3H, s), 2.52 - 2.75 (1H, m), 2.86 - 2.97 (2H, m), 3.30 - 3.60 (14H, m), 3.80 (2H, t, J = 5.0 Hz), 3.98 - 4.09 (2H, m), 4.16 (2H, t, J = 4.9 Hz), 6.94 - 7.03 (3H, m), 7.30 (2H, d, J = 8.4 Hz), 7.36 - 7.57 (8H, m).

IR (KBr) 3323, 1638, 1607, 1516, 1501, 1406, 1314, 1244, 1123 cm<sup>-1</sup>.

Anal. Calcd. C<sub>41</sub>H<sub>55</sub>N<sub>3</sub>O<sub>5</sub> Calcd. C, 73.51; H, 8.28; N, 6.27. Found C, 73.60; H, 8.16; N, 6.23.

#### Working Example 107 (Production of Compound 107)

To a solution of 7-[4-(2-butoxyethoxy)phenyl]-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]-2,3-dihydro-1H-1-

10018321-121201

benzazepine-4-carboxylic acid (300mg) in THF (10ml) were added thionyl chloride (0.068ml) and DMF (one droplet) at room temperature, and the mixture was stirred for 1 hour. The reaction mixture was added dropwise to a solution of 5 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (151mg) and triethylamine (0.7ml) in THF (3ml) at 0°C. The mixture was stirred at room temperature for 20 hours, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with 10 saturated brine, and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column chromatography (ethanol : ethyl acetate = 1 : 19 → 1 : 10), and the resulting crystals were purified by recrystallization 15 (ethyl acetate-diisopropyl ether) to give 7-[4-(2-butoxyethoxy)phenyl]-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]-N-[4-[[N-methyl-N-tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 107) (144mg) as yellow crystals. 20 mp 123 - 126°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.3 Hz), 1.31 - 1.47 (5H, m), 1.51 - 1.83 (6H, m), 2.21 (3H, s), 2.54 - 2.73 (1H, m), 2.86 - 2.97 (2H, m), 3.28 - 3.60 (10H, m), 3.80 (2H, t, J = 5.0 Hz), 3.93 - 4.09 (6H, m), 4.16 (2H, t, 25 J = 5.0 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.26 - 7.32 (3H, m),



7.39 - 7.50 (8H, m).

IR (KBr) 3245, 1645, 1607, 1516, 1499, 1406, 1316, 1244, 1175, 1140, 1046  $\text{cm}^{-1}$ .

Anal. Calcd.  $\text{C}_{41}\text{H}_{53}\text{N}_3\text{O}_5 \cdot 0.25\text{H}_2\text{O}$  Calcd. C, 71.54; H, 7.83; N,

5 6.10. Found C, 71.49; H, 7.96; N, 6.03.

Working Example 108 (Production of Compound 108)

A mixture of 7-[4-(2-butoxyethoxy)phenyl]-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-  
 10 1H-1-benzazepine-4-carboxamide (100mg), cerium chloride heptahydrate (300mg), sodium iodide (19mg) and acetonitrile (5ml) was stirred at 60°C for 5 days. Water was added to the reaction system, and the mixture was extracted with ethyl acetate. The organic layer was  
 15 washed with saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column chromatography (ethanol : ethyl acetate = 1 : 3) to give  
 20 7-[4-(2-butoxyethoxy)phenyl]-1-(2-oxopropyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 108) (52mg) as yellow crystals.

$^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (3H, t,  $J = 7.3$  Hz), 1.32 - 1.47 (2H, m), 1.53 - 2.05 (6H, m), 2.26 (3H, s), 2.38 (3H, s),  
 25 s), 3.29 - 3.47 (4H, m), 3.55 (2H, t,  $J = 6.6$  Hz), 3.74 -

10018321.124201

3.86 (4H, m), 4.01 - 4.21 (6H, m), 6.54 (1H, d,  $J = 8.0$  Hz),  
6.98 (2H, d,  $J = 8.8$  Hz), 7.26 - 7.67 (10H, m).

IR (KBr) 3302, 1728, 1651, 1607, 1518, 1501, 1244, 914  $\text{cm}^{-1}$ .

Working Example 109 (Production of Compound 109)

- 5 To a solution of 7-[4-(2-butoxyethoxy)phenyl]-1-propyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (16.4g) in ethyl acetate (1500ml) was added  
10 4N hydrochloric acid-ethyl acetate (25ml) at room temperature, and the mixture was stirred for 1 hour. The precipitated crystals were collected by filtration, which was purified by recrystallization (2-propanol) to give 7-[4-(2-butoxyethoxy)phenyl]-1-propyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-  
15 1H-1-benzazepine-4-carboxamide dihydrochloride (Compound 109) (8.61g) as pale yellow crystals.
- $^1\text{H}$ -NMR (200 MHz,  $\text{DMSO-d}_6$ )  $\delta$  0.88 (3H, t,  $J = 7.1$  Hz), 0.94 (3H, t,  $J = 7.3$  Hz), 1.22 - 2.18 (10H, m), 2.57 (3H, s), 2.78 - 2.90 (2H, m), 3.21 - 3.41 (7H, m), 3.46 (2H, t,  $J =$   
20 6.4 Hz), 3.68 - 3.73 (2H, m), 3.91 - 4.15 (5H, m), 4.35 - 4.60 (1H, m), 6.97 - 7.02 (3H, m), 7.42 - 7.58 (6H, m), 7.65 (1H, s), 7.81 (2H, d,  $J = 8.4$  Hz), 10.03 (1H, s), 10.45 - 10.59 (1H, m).
- IR (KBr) 3248, 1663, 1609, 1521, 1501, 1464, 1312, 1248,  
25 1180, 1121, 831  $\text{cm}^{-1}$ .

10018331.1241201

Anal. Calcd.  $C_{39}H_{53}N_3O_4Cl_2$  Calcd. C, 67.04; H, 7.65; N, 6.01.

Found C, 67.10; H, 7.51; N, 6.14.

Working Example 110 (Production of Compound 110)

To a solution of 7-[4-(2-butoxyethoxy)phenyl]-1-propyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (2.0g) in ethanol (150ml) was added fumaric acid (371mg) at room temperature, and the mixture was stirred for 0.5 hour. After concentration under reduced pressure, to the residue was added ethyl acetate, and the precipitated crystals were collected by filtration, which was purified by recrystallization (2-propanol) to give 7-[4-(2-butoxyethoxy)phenyl]-1-propyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide fumarate (Compound 110) (1.86g) as yellow crystals.

mp 159 - 161°C.

$^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  0.93 (3H, t,  $J = 7.3$  Hz), 0.99 (3H, t,  $J = 7.2$  Hz), 1.30 - 1.45 (2H, m), 1.51 - 1.86 (8H, m), 2.24 (3H, s), 2.61 - 2.79 (1H, m), 2.86 - 2.95 (2H, m), 3.24 - 3.43 (6H, m), 3.55 (2H, t,  $J = 6.4$  Hz), 3.62 (2H, s), 3.81 (2H, t,  $J = 5.0$  Hz), 3.98 - 4.09 (2H, m), 4.16 (2H, t,  $J = 5.0$  Hz), 6.90 (1H, d,  $J = 8.8$  Hz), 6.98 (2H, d,  $J = 8.8$  Hz), 7.26 - 7.57 (12H, m).

IR (KBr) 3365, 1653, 1609, 1520, 1501, 1316, 1246, 1177 $cm^{-1}$ .

Anal. Calcd.  $C_{43}H_{55}N_3O_8$  Calcd. C, 69.61; H, 7.47; N, 5.66.

Found C, 69.51; H, 7.46; N, 5.88.

Reference Example 294

To a solution of methyl 7-bromo-2,3-dihydro-1H-1-  
5 benzazepine-4-carboxylate (0.80g) and 3-  
methoxypropionaldehyde (1.25g) in 1,2-dichloroethane  
(10ml) was added sodium triacetoxyborohydride (1.81g) at  
room temperature, and the mixture was stirred for 24  
hours. Water was added to the reaction system, and the  
10 mixture was extracted with ethyl acetate. The organic  
layer was washed with saturated brine and dried with  
magnesium sulfate. After concentration under reduced  
pressure, the resulting residue was separated and  
purified with column chromatography (ethyl acetate :  
15 hexane = 1 : 3 → 1 : 2) to give methyl 7-bromo-1-(3-  
methoxypropyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate  
(935mg) as yellow oil.

$^1H$ -NMR (200 MHz,  $CDCl_3$ )  $\delta$  1.83 - 1.96 (2H, m), 2.79 (2H, t,  
J = 4.0 Hz), 3.22 (2H, t, J = 4.9 Hz), 3.34 (3H, s), 3.37 -  
20 3.45 (4H, m), 3.80 (3H, s), 6.75 (1H, d, J = 9.2 Hz), 7.21  
- 7.26 (1H, m), 7.42 (1H, d, J = 2.6 Hz), 7.57 (1H, s).  
IR (neat) 1699, 1626, 1588, 1539, 1495, 1435, 1256, 1177,  
1117, 1086  $cm^{-1}$ .

Reference Example 295

25 A mixture of methyl 7-bromo-1-(3-methoxypropyl)-2,3-

10018391-121201

dihydro-1H-1-benzazepine-4-carboxylate (450mg), 4-(2-propoxyethoxy)phenyl borate (313mg) and potassium carbonate (351mg) in toluene-ethanol-water (15-1.5-1.5ml) was stirred at room temperature for 1 hour under argon atmosphere. To the reaction system was added tetrakis(triphenylphosphine)palladium (73mg), and the mixture was heated to reflux for 20 hours. After cooled to room temperature, the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column chromatography (ethyl acetate : hexane = 1 : 4 → 1 : 2) to give methyl 1-(3-methoxypropyl)-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (376mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.3 Hz), 1.55 - 1.73 (2H, m), 1.86 - 2.03 (2H, m), 2.79 - 2.84 (2H, m), 3.26 - 3.31 (2H, m), 3.36 (3H, s), 3.42 - 3.55 (6H, m), 3.81 (3H, s), 3.83 (2H, t, J = 4.9 Hz), 4.16 (2H, t, J = 4.9 Hz), 6.92 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz), 7.38 - 7.51 (4H, m), 7.76 (1H, s).

IR (neat) 1699, 1607, 1505, 1456, 1435, 1244, 1181, 1119 cm<sup>-1</sup>.

## Reference Example 296

To a solution of methyl 1-(3-methoxypropyl)-7-[4-(2-

propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (376mg) in a mixture of THF-methanol (5-10ml) was added 1N sodium hydroxide solution (3.0ml) at room temperature, and the mixture was stirred at 50°C for 24 hours. After concentration under reduced pressure, 1N hydrochloric acid was added to pH 3-4, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the resulting crystals were collected by filtration. The crystals were washed with diisopropyl ether and hexane to give 1-(3-methoxypropyl)-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (346mg) as yellow crystals.

mp 114 - 115°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.94 (3H, t, J = 7.3 Hz), 1.56 - 1.73 (2H, m), 1.88 - 2.04 (2H, m), 2.78 - 2.89 (2H, m), 3.24 - 3.35 (2H, m), 3.36 (3H, s), 3.43 - 3.55 (6H, m), 3.81 (2H, t, J = 5.0 Hz), 4.17 (2H, t, J = 5.0 Hz), 6.94 (1H, d, J = 8.4 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.40 - 7.53 (4H, m), 7.88 (1H, s).

IR (KBr) 1671, 1607, 1501, 1273, 1252, 1186, 1115 cm<sup>-1</sup>.

Anal. Calcd. C<sub>26</sub>H<sub>33</sub>NO<sub>5</sub> Calcd. C, 71.05; H, 7.57; N, 3.19.

Found C, 70.78; H, 7.38; N, 3.01.

A mixture of methyl 7-bromo-1-(3-methoxypropyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (478.2mg), 4-(2-butoxyethoxy)phenyl borate (354mg) and potassium carbonate (373mg) in toluene-ethanol-water (15-1.5-1.5ml) was stirred at room temperature for 1 hour under argon atmosphere. To the reaction system was added tetrakis(triphenylphosphine)palladium (78mg), and the mixture was heated to reflux for 16 hours. After cooled to room temperature, the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column chromatography (ethyl acetate : hexane = 1 : 4 → 1 : 3 → 1 : 2) to give an end product (362mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.3 Hz), 1.30 - 1.49 (2H, m), 1.53 - 1.69 (2H, m), 1.87 - 2.03 (2H, m), 2.78 - 2.86 (2H, m), 3.28 (2H, t, J = 4.8 Hz), 3.36 (3H, s), 3.42 - 3.50 (4H, m), 3.55 (2H, t, J = 6.7 Hz), 3.78 - 3.83 (5H, m), 4.16 (2H, t, J = 5.0 Hz), 6.90 - 7.00 (3H, m), 7.38 - 7.51 (4H, m), 7.76 (1H, s).

IR (neat) 1699, 1622, 1607, 1505, 1456, 1435, 1246, 1182, 1119, 818 cm<sup>-1</sup>.

#### Reference Example 298

To a solution of methyl 7-[4-(2-

butoxyethoxy)phenyl]-1-(3-methoxypropyl)-2,3-dihydro-1H-  
1-benzazepine-4-carboxylate (362.3mg) in a mixture of  
THF-methanol (5-10ml) was added 1N sodium hydroxide  
solution (2.8ml) at room temperature, and the mixture was  
5 stirred at 50°C for 15 hours. After concentration under  
reduced pressure, 1N hydrochloric acid was added to pH 3-  
4, and the mixture was extracted with ethyl acetate. The  
organic layer was washed with saturated brine and dried  
with magnesium sulfate. After concentration under  
10 reduced pressure, the resulting crystals were collected  
by filtration. The crystals were washed with diisopropyl  
ether and hexane to give 7-[4-(2-butoxyethoxy)phenyl]-1-  
(3-methoxypropyl)-2,3-dihydro-1H-1-benzazepine-4-  
carboxylic acid (283mg) as yellow crystals.  
15 mp 99 - 101°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.29 -  
1.48 (2H, m), 1.53 - 1.70 (2H, m), 1.88 - 2.04 (2H, m),  
2.80 - 2.89 (2H, m), 3.25 - 3.35 (2H, m), 3.37 (3H, s),  
3.43 - 3.49 (4H, m), 3.56 (2H, t, J = 6.6 Hz), 3.81 (2H, t,  
20 J = 5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.94 (1H, d, J = 8.6  
Hz), 6.98 (2H, d, J = 8.4 Hz), 7.40 - 7.53 (4H, m), 7.88  
(1H, s).

IR (KBr) 1671, 1607, 1501, 1269, 1246, 1184, 1115 cm<sup>-1</sup>.

Anal. Calcd. C<sub>27</sub>H<sub>35</sub>NO<sub>5</sub> Calcd. C, 71.50; H, 7.78; N, 3.09.  
25 Found C, 71.31; H, 7.75; N, 2.99.

10018321.121201



## Reference Example 299

To a solution of methyl 7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (400mg) and 3-ethoxypropionaldehyde (0.53g) in 1,2-dichloroethane (10ml) was added sodium triacetoxymethylborohydride (0.66g) at room temperature, and the mixture was stirred for 20 hours. To the reaction system was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column chromatography (ethyl acetate : hexane = 1 : 4 → 1 : 3) to give methyl 1-(3-ethoxypropyl)-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (475mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J = 7.5 Hz), 1.23 (3H, t, J = 6.9 Hz), 1.52 - 1.72 (2H, m), 1.88 - 2.03 (2H, m), 2.80 - 2.84 (2H, m), 3.26 - 3.31 (2H, m), 3.43 - 3.55 (8H, m), 3.79 - 3.84 (5H, m), 4.16 (2H, t, J = 5.0 Hz), 6.94 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.40 (1H, dd, J = 8.8, 2.2 Hz), 7.47 (2H, d, J = 8.8 Hz), 7.51 (1H, d, J = 2.2 Hz), 7.76 (1H, s).

## Reference Example 300

To a solution of methyl 1-(3-ethoxypropyl)-7-[4-(2-

propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (475mg) in a mixture of THF-methanol (5-10ml) was added 1N sodium hydroxide solution (3.0ml) at room temperature, and the mixture was stirred at 50°C for 62  
5 hours. After concentration under reduced pressure, to the mixture was added 1N hydrochloric acid (3.0ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. After concentration under  
10 reduced pressure, the resulting crystals were collected by filtration. The crystals were washed with diisopropyl ether and hexane to give 1-(3-ethoxypropyl)-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (390mg) as yellow crystals.

15 mp 98 - 100°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.95 (3H, t, J = 7.0 Hz), 1.23 (3H, t, J = 7.2 Hz), 1.53 - 1.74 (2H, m), 1.89 - 2.04 (2H, m), 2.79 - 2.89 (2H, m), 3.26 - 3.35 (2H, m), 3.44 - 3.55 (8H, m), 3.81 (2H, t, J = 5.0 Hz), 4.17 (2H, t, J = 5.0 Hz),  
20 6.96 (1H, d, J = 8.4 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.39 - 7.52 (4H, m), 7.87 (1H, s).

IR (KBr) 1669, 1607, 1501, 1275, 1248, 1184, 1125 cm<sup>-1</sup>.

Anal. Calcd. C<sub>27</sub>H<sub>35</sub>NO<sub>5</sub> Calcd. C, 71.50; H, 7.78; N, 3.09.

Found C, 71.23; H, 7.84; N, 3.16.

25 Reference Example 301

To a solution of methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (400mg) and 3-ethoxypropionaldehyde (0.52g) in 1,2-dichloroethane (10ml) was added sodium triacetoxymethylborohydride (0.64g) at room temperature, and the mixture was stirred for 20 hours. To the reaction system was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column chromatography (ethyl acetate : hexane = 1 : 4 → 1 : 3) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(3-ethoxypropyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (452mg) as yellow oil.

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (3H, t,  $J = 7.2$  Hz), 1.23 (3H, t,  $J = 7.1$  Hz), 1.28 - 1.68 (4H, m), 1.89 - 2.06 (2H, m), 2.78 - 2.87 (2H, m), 3.27 - 3.31 (2H, m), 3.43 - 3.59 (8H, m), 3.78 - 3.83 (5H, m), 4.16 (2H, t,  $J = 4.9$  Hz), 6.94 (1H, d,  $J = 8.4$  Hz), 6.98 (2H, d,  $J = 8.8$  Hz), 7.37 - 7.52 (4H, m), 7.76 (1H, s).

IR (neat) 1699, 1622, 1609, 1501, 1454, 1435, 1373, 1354, 1246, 1181, 1125, 818  $\text{cm}^{-1}$ .

## Reference Example 302

To a solution of methyl 7-[4-(2-

butoxyethoxy)phenyl]-1-(3-ethoxypropyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (452mg) in a mixture of THF-methanol (5-10ml) was added 1N sodium hydroxide solution (3.0ml) at room temperature, and the mixture was stirred  
5 at 50°C for 40 hours. After concentration under reduced pressure, to the mixture was added 1N hydrochloric acid (3.0ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. After concentration under  
10 reduced pressure, the resulting crystals were collected by filtration. The crystals were washed with hexane to give 7-[4-(2-butoxyethoxy)phenyl]-1-(3-ethoxypropyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (340mg) as yellow crystals.

15 mp 76 - 78°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.4 Hz), 1.23 (3H, t, J = 7.0 Hz), 1.30 - 1.47 (2H, m), 1.53 - 1.68 (2H, m), 1.88 - 2.04 (2H, m), 2.79 - 2.88 (2H, m), 3.26 - 3.37 (2H, m), 3.44 - 3.59 (8H, m), 3.81 (2H, t, J = 4.9 Hz), 4.16 (2H, t, J = 4.9 Hz), 6.96 (1H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.40 - 7.54 (4H, m), 7.88 (1H, s).

20 IR (KBr) 1667, 1607, 1501, 1271, 1248, 1184, 1125 cm<sup>-1</sup>.

Anal. Calcd. C<sub>28</sub>H<sub>37</sub>NO<sub>5</sub> Calcd. C, 71.92; H, 7.98; N, 3.00.

Found C, 71.89; H, 8.08; N, 2.68.

25 Reference Example 303

100183724-121204

A mixture of palladium chloride (96mg) and cuprous chloride (218mg) in DMF-water (7-1ml) was stirred at 60°C for 18 hours under oxygen atmosphere. To the reaction system was added a solution of methyl 7-bromo-1-(2-propenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (500mg) in DMF-water (7-1ml) was added, and the mixture was stirred at 60°C for 7 hours. To the reaction system was added saturated brine, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column chromatography (ethyl acetate : hexane = 1 : 4 → 1 : 2) to give methyl 7-bromo-1-(2-oxopropyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (311mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 2.21 (3H, s), 2.82 (2H, t, J = 4.6 Hz), 3.30 (2H, t, J = 4.6 Hz), 3.81 (3H, s), 4.08 (2H, s), 6.31 (1H, d, J = 8.8 Hz), 7.21 (1H, dd, J = 8.8, 2.2 Hz), 7.46 (1H, d, J = 2.2 Hz), 7.59 (1H, s).

20 Reference Example 304

A solution of methyl 7-bromo-1-(2-oxopropyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.29g), ethylene glycol (2.3g) and p-toluenesulfonic acid monohydrate (36mg) in toluene (10ml) was heated to reflux for 3 days while removing water. After cooled to room temperature,

an aqueous solution of sodium hydrogen carbonate was added to alkaline, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column chromatography (ethyl acetate : hexane = 1 : 4) to give methyl 7-bromo-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (992mg).

mp 96 - 99°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.57 (3H, s), 2.78 - 2.83 (2H, m), 3.34 - 3.39 (2H, m), 3.43 (2H, s), 3.80 (3H, s), 3.88 - 3.99 (4H, m), 7.13 (1H, d, J = 9.2 Hz), 7.22 - 7.27 (1H, m), 7.42 (1H, d, J = 2.2 Hz), 7.58 (1H, s).

IR (KBr) 1703, 1626, 1495, 1435, 1258, 1217, 1179, 1086, 1047 cm<sup>-1</sup>.

Anal. Calcd. C<sub>17</sub>H<sub>20</sub>NO<sub>4</sub>Br Calcd. C, 53.42; H, 5.27; N, 3.66.

Found C, 53.34; H, 5.50; N, 3.64.

#### Reference Example 305

A mixture of methyl 7-bromo-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (960mg), 4-(2-butoxyethoxy)phenyl borate (0.66g) and potassium carbonate (0.69g) in a mixture of toluene-ethanol-water (25-2.5-2.5ml) was stirred at room temperature for 1 hour under argon atmosphere. To the

reaction system was added

tetrakis(triphenylphosphine)palladium (144mg), and the mixture was heated to reflux for 8 hours. After cooled to room temperature, the mixture was extracted with ethyl acetate, and the mixture was dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column chromatography to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzaepine-4-carboxylate (796mg) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.4 Hz), 1.31 - 1.47 (5H, m), 1.52 - 1.67 (2H, m), 1.78 - 1.86 (2H, m), 3.41 - 3.45 (2H, m), 3.49 (2H, s), 3.56 (2H, t, J = 6.6 Hz), 3.78 - 3.83 (5H, m), 3.97 (4H, s), 4.16 (2H, t, J = 5.0 Hz), 6.98 (2H, d, J = 8.8 Hz), 7.26 - 7.30 (1H, m), 7.39 - 7.51 (4H, m), 7.77 (1H, s).

IR (neat) 1699, 1609, 1505, 1495, 1435, 1242, 1181, 1127, 1047 cm<sup>-1</sup>.

Reference Example 306

To a solution of methyl 7-[4-(2-butoxyethoxy)phenyl]-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzaepine-4-carboxylate (795.7mg) in a mixture of THF-methanol (5-5ml) was added 1N sodium hydroxide solution.

Amen.  
B56

10018334 121201

(3.2ml) at room temperature, and the mixture was stirred at 50°C for 16 hours. After concentration under reduced pressure, to the mixture was added 1N hydrochloric acid (4ml) and the mixture was extracted with ethyl acetate.

5 The organic layer was washed with saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the resulting crystals were collected by filtration. The crystals were washed with diisopropyl ether to give 7-[4-(2-butoxyethoxy)phenyl]-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (664mg) as yellow crystals.

mp 127 - 129°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.4 Hz), 1.30 - 1.49 (5H, m), 1.52 - 1.68 (2H, m), 2.81 - 2.89 (2H, m), 3.41 - 3.49 (2H, m), 3.51 (2H, s), 3.56 (2H, t, J = 6.6 Hz), 3.81 (2H, t, J = 5.0 Hz), 3.91 - 4.01 (4H, m), 4.17 (2H, t, J = 5.0 Hz), 6.98 (2H, t, J = 8.8 Hz), 7.26 - 7.32 (1H, m), 7.41 - 7.53 (4H, m), 7.89 (1H, s).

20 IR (KBr) 1665, 1611, 1503, 1427, 1246, 1184, 1046 cm<sup>-1</sup>.

Anal. Calcd. C<sub>28</sub>H<sub>35</sub>NO<sub>6</sub> Calcd. C, 69.83; H, 7.33; N, 2.91.

Found C, 69.78; H, 7.39; N, 2.81.

#### Reference Example 307

To a solution of 7-bromo-2,3,4,5-tetrahydro-1H-1-benzazepine-5-one (5.0g), propionaldehyde (15ml) and



acetic acid (4.7ml) in 1,2-dichloroethane (250ml) was added sodium triacetoxymethylborohydride (22.0g) at room temperature, and the mixture was stirred for 6 hours. To the reaction system was added water, and the mixture was  
5 extracted with ethyl acetate. The organic layer was washed with an aqueous solution of sodium hydrogen carbonate and saturated brine, and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column  
10 chromatography (ethyl acetate : hexane = 1 : 4) to give 7-bromo-1-propyl-2,3,4,5-tetrahydro-1H-1-benzazepine-5-one (5.89g) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.00 (3H, t, J = 7.4 Hz), 1.58 - 1.81 (2H, m), 2.18 - 2.33 (2H, m), 2.75 (2H, t, J = 7.2 Hz),  
15 3.26 (2H, t, J = 6.6 Hz), 3.38 (2H, t, J = 7.7 Hz), 6.76 (1H, d, J = 9.0 Hz), 7.34 (1H, dd, J = 9.0, 2.6 Hz), 7.84 (1H, d, J = 2.6 Hz).

IR (neat) 1667, 1590, 1487, 1443, 1412, 1381, 1366, 1337, 1296, 1281, 1252, 1223, 1206, 1161, 1136, 1117, 808 cm<sup>-1</sup>.

20           Reference Example 308

A mixture of 7-bromo-1-propyl-2,3,4,5-tetrahydro-1H-1-benzazepine-5-one (5.89g), 4-(2-butoxyethoxy)phenyl borate (5.45g) and potassium carbonate (5.74g) in toluene-ethanol-water (200-20-20ml) was stirred at room  
25 temperature for 1 hour under argon atmosphere. To the

reaction system was added

tetrakis(triphenylphosphine)palladium (0.72g), and the mixture was heated to reflux for 3 hours. After cooled to room temperature, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with column chromatography (ethyl acetate : hexane = 1 : 9 → 1 : 4) to give 7-[4-(2-butoxyethoxy)phenyl]-1-propyl-2,3,4,5-tetrahydro-1H-1-benzazepine-5-one (7.15g) as yellow oil.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.3 Hz), 1.02 (3H, t, J = 7.5 Hz), 1.29 - 1.47 (2H, m), 1.52 - 1.84 (4H, m), 2.18 - 2.35 (2H, m), 2.80 (2H, t, J = 7.1 Hz), 3.31 (2H, t, J = 6.6 Hz), 3.44 (2H, t, J = 7.5 Hz), 3.55 (2H, t, J = 6.8 Hz), 3.80 (2H, t, J = 4.9 Hz), 4.15 (2H, t, J = 4.9 Hz), 6.92 - 6.98 (3H, m), 7.46 - 7.54 (3H, m), 7.96 (1H, d, J = 2.6 Hz).

#### Reference Example 309

To a solution of 7-[4-(2-butoxyethoxy)phenyl]-1-propyl-2,3,4,5-tetrahydro-1H-1-benzazepine-5-one (500mg) in THF (15ml) was added dropwise lithium bis(trimethylsilyl)amide (1.0M solution in hexane, 3.8ml) at -78°C under argon atmosphere. After stirred at -78°C for 2 hours, argon was removed under reduced pressure to

replace it with carbon dioxide. The reaction mixture was removed from an acetone-dry ice bath, and stirred at room temperature for 2 hours. To the reaction system were added water and ethyl acetate, and 1N hydrochloric acid was slowly added at 0°C until pH 6. The mixture was extracted with ethyl acetate, the organic layer was washed with saturated brine and dried with magnesium sulfate. Concentration by rotary evaporator under reduced pressure afforded yellow oil (981mg).

To a solution of the oil (980.9mg) in ethanol (20ml) was added sodium borohydride (0.48g), and the mixture was stirred at room temperature for 2 hours under nitrogen atmosphere. Ethanol was evaporated under reduced pressure, and water and ethyl acetate were added thereto.

1N hydrochloric acid was slowly added at 0°C until pH 6. The mixture was extracted with ethyl acetate, and the extract was washed with saturated brine and dried with magnesium sulfate. After concentration by rotary evaporator under reduce pressure, concentrated

hydrochloric acid (1.5ml) was added to a solution of the e residue (769mg) in 1,2-dimethoxyethane (20ml) at room temperature, and the mixture was heated to reflux for 1 hour. After cooled to room temperature, water and ethyl acetate were added thereto. 1N sodium hydroxide solution

was added dropwise at 0°C until pH=4. The mixture was

10018321.121201

extracted with ethyl acetate, and water was added to the organic layer, followed by addition of 1N sodium hydroxide solution until pH 6. The solution was separated, and the organic layer was washed with water and saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the residue was separated and purified with silica gel column chromatography (ethyl acetate : hexane = 1 : 2 → 1 : 1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-propyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (374mg).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.96 - 1.02 (6H, m), 1.34 - 1.45 (2H, m), 1.54 - 1.80 (4H, m), 2.84 (2H, m), 3.28 - 3.35 (4H, m), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.88 (1H, d, J = 8.8 Hz), 6.98 (2H, t, J = 8.8 Hz), 7.39 - 7.52 (4H, m), 7.88 (1H, s).

#### Reference Example 310

To a solution of methyl 7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.0g, 2.53mmol) and propionaldehyde (1ml, 13.86mmol) in 1,2-dichloroethane (30ml) was added sodium triacetoxymethylborohydride (1.9g, 8.96mmol) at room temperature, and the mixture was stirred for 24 hours. To the reaction system was added 1N sodium hydroxide solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and

- saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in THF (50ml) and methanol (50ml), and to the solution was added 1N sodium hydroxide solution. After heating to reflux for 1 hour, the mixture was concentrated under reduced pressure. To the residue was added 1N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. After concentration under reduced pressure, the resulting crystals were collected by filtration to give 7-[4-(2-butoxyethoxy)phenyl]-1-propyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.895g) as yellow crystals. mp 145 - 146°C.
- <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.96 - 1.02 (6H, m), 1.34 - 1.45 (2H, m), 1.54 - 1.80 (4H, m), 2.84 (2H, m), 3.28 - 3.35 (4H, m), 3.55 (2H, t, J = 6.6 Hz), 3.80 (2H, t, J = 5.0 Hz), 4.16 (2H, t, J = 5.0 Hz), 6.88 (1H, d, J = 8.8 Hz), 6.98 (2H, t, J = 8.8 Hz), 7.39 - 7.52 (4H, m), 7.88 (1H, s).
- IR (KBr) 2975, 2925, 2870, 1670, 1605, 1500 cm<sup>-1</sup>.
- Anal. Calcd. C<sub>26</sub>H<sub>33</sub>NO<sub>4</sub> Calcd. C, 73.73; H, 7.85; N, 3.31. Found C, 73.68; H, 8.11; N, 3.23.

~~Reference Example 311~~

- ~~4-morpholinophenyl borate (237mg) and 7-bromo-1-propyl-N-[4-[[N-methyl-N-(terahydropyran-4-~~

Amen.  
B57

10018321.121201

yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (391mg) were dissolved in water : ethanol : toluene (= 1 : 1 : 10, v/v, 18.0ml), and potassium carbonate (253mg) was added thereto. This mixture was stirred at room temperature for 30 minutes under argon atmosphere, tetrakis(triphenylphosphine)palladium (35mg) was added thereto, and the mixture was heated to reflux for 10 hours under argon atmosphere. The reaction mixture was diluted with ethyl acetate, and washed with water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified with silica gel column chromatography (ethyl acetate → ethyl acetate:ethanol = 10:1), which was further recrystallized from ethyl acetate-diisopropyl ether-hexane to give N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-morpholinophenyl)-1-propyl-2,3-dihydro-1-benzazepine-4-carboxamide (222mg) as yellow crystals.

mp 114 - 118°C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.99 (3H, t, J = 7.4 Hz), 1.64 - 1.81 (6H, m), 2.21 (3H, s), 2.57 - 2.70 (1H, m), 2.92 (2H, t, J = 4.8 Hz), 3.20 (4H, t, J = 4.8 Hz), 3.28 - 3.43 (6H, m), 3.57 (2H, s), 3.89 (4H, t, J = 4.8 Hz), 4.01 - 4.07 (2H, m), 6.90 (1H, d, J = 8.8 Hz), 6.97 (2H, d, J = 8.8 Hz),

7.30 (2H, d,  $J = 8.8$  Hz), 7.39 - 7.56 (8H, m).

IR (KBr) 2955, 1649, 1605, 1512, 1503, 1451, 1406, 1312, 1233, 1175, 1119, 928, 812, 733  $\text{cm}^{-1}$ .

Anal. Calcd. for  $\text{C}_{37}\text{H}_{45}\text{N}_4\text{O}_3$  ( $1.1\text{H}_2\text{O}$ ): C, 72.31; H, 7.90; N, 9.12. Found C, 72.09; H, 7.66; N, 8.87.

#### Reference Example 312

One droplet of DMF was added to a solution of 1-(2-methoxybenzyl)-7-(4-propoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (340mg) in tetrahydrofuran (10ml). Then, thionyl chloride (267mg) was added thereto at  $0^\circ\text{C}$ , the temperature was returned to room temperature, and the mixture was stirred for 1 hour under nitrogen atmosphere. The solvent and excess thionyl chloride were evaporated under reduced pressure, and the resulting residue was suspended in tetrahydrofuran (30ml), which was added to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (197mg) and triethylamine (906mg) in tetrahydrofuran (10ml) at  $0^\circ\text{C}$ . The mixture was stirred at room temperature for 1 hour under nitrogen atmosphere, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography

(methanol : ethyl acetate = 1 : 8), which was recrystallized from hexane-ethyl acetate to give 1-(2-methoxybenzyl)-N-[4-[[N-methyl N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-7-(4-propoxyphenyl)-2,3-dihydro-  
 5 1-benzazepine-4-carboxamide (337mg) as yellow crystals.  
<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.05 (t, 3H, J = 7.2 Hz), 1.60 - 1.88 (m, 6H), 2.21 (s, 3H), 2.64 (br, 1H), 2.90 (br, 2H), 3.32 - 3.45 (m, 4H), 3.57 (s, 2H), 3.89 (s, 3H), 3.92 - 4.08 (m, 4H), 4.59 (s, 2H), 6.82 (d, 1H, J = 8.8 Hz), 6.92  
 10 - 6.97 (m, 4H), 7.15 - 7.22 (m, 1H), 7.26 - 7.38 (m, 4H), 7.44 - 7.60 (m, 7H).

#### Reference Example 313

One droplet of DMF was added to a solution of 1-[(1-ethylpyrazol-4-yl)methyl]-7-(4-propoxyphenyl)-2,3-  
 15 dihydro-1-benzazepine-4-carboxylic acid (330mg) in dichloromethane (15ml). Then, thionyl chloride (118mg) was added thereto at 0°C, the temperature was returned to room temperature, and the mixture was stirred for 1 hour under nitrogen atmosphere. Then, this solution was added  
 20 to a solution of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (219mg) and triethylamine (2.01g) in dichloromethane (15ml) at 0°C. The mixture was stirred at room temperature for overnight under nitrogen atmosphere, water was added thereto, and the mixture was  
 25 extracted with ethyl acetate. The organic layer was



washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography

5 (methanol : ethyl acetate = 1 : 4), which was recrystallized from hexane-ethyl acetate to give 1-[(1-ethylpyrazol-4-yl)methyl]-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-7-(4-propoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxamide  
10 (362mg) as yellow crystals.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 1.05 (t, 3H, J = 7.4 Hz), 1.49 (t, 3H, J = 7.4 Hz), 1.58 - 1.88 (m, 6H), 2.21 (s, 3H), 2.65 (br, 1H), 2.84 (br, 2H), 3.25 - 3.42 (m, 4H), 3.57 (s, 2H), 3.93 - 4.06 (m, 4H), 4.16 (q, 2H, J = 7.4 Hz), 4.40 (s, 2H),  
15 6.94 - 7.01 (m, 3H), 7.26 - 7.40 (m, 4H), 7.45 - 7.56 (m, 8H).

Anal. Calcd. C<sub>39</sub>H<sub>47</sub>N<sub>5</sub>O<sub>3</sub> Calcd. C, 73.90; H, 7.47; N, 11.05.  
Found C, 73.58; H, 7.47; N, 10.86.

#### Reference Example 314

20 Methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(tetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (1.9g) was dissolved in acetonitrile (190ml). To the solution were added potassium carbonate (1.65g) and ethyl iodide (0.76ml), and the mixture was stirred at 50°C for 16  
25 hours. The solvent was concentrated to 1/3 under reduced

10018321.121201

pressure, which was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate.

The solvent was removed under reduced pressure, and the  
 5 resulting residue was purified with silica gel column chromatography (hexane/ethyl acetate=3/1  $\rightarrow$  1/2) to give methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(1-ethyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (1.05g) and methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(2-  
 10 ethyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.42g).

<sup>1</sup>H-NMR (1-ethyl compound; 200 MHz, CDCl<sub>3</sub>)  $\delta$  0.93 (3H, t, J = 7.2 Hz), 1.33 - 1.45 (2H, m), 1.44 (3H, t, J = 7.0 Hz), 1.47 - 1.66 (2H, m), 2.58 (2H, t, J = 4.6 Hz), 3.37 (2H, t, J = 5.0 Hz), 3.56 (2H, t, J = 6.6 Hz), 3.78 - 3.84 (2H, m),  
 15 3.81 (3H, s), 4.13 - 4.19 (2H, m), 4.31 (2H, q, J = 7.0 Hz), 4.84 (2H, s), 6.95 - 7.02 (3H, m), 7.42 - 7.49 (3H, m), 7.57 (1H, m), 7.78 (1H, s).

<sup>1</sup>H-NMR (2-ethyl compound; 200 MHz, CDCl<sub>3</sub>)  $\delta$  0.93 (3H, t, J = 7.0 Hz), 1.33 - 1.49 (2H, m), 1.57 - 1.65 (2H, m), 1.65 (3H, t, J = 7.4 Hz), 2.83 - 2.91 (2H, m), 3.39 - 3.45 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.78 - 3.83 (2H, m), 3.82 (3H, s), 4.07 - 4.18 (2H, m), 4.67 (2H, q, J = 7.4 Hz), 4.75 (2H, s), 6.98 (2H, d, J = 8.8 Hz), 7.16 (1H, d, J = 8.4 Hz),  
 20 7.40 - 7.54 (4H, m), 7.79 (1H, s).

## Reference Example 315

Methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(1-ethyltetrazol-4-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.11g) was dissolved in THF (2.2ml)/methanol (2.2ml). To the solution was added 1N sodium hydroxide (1.1ml), and the mixture was stirred at 50°C for 4 hours. After cooled to room temperature, pH was adjusted to approximate 5 with 6N hydrochloric acid, and the solvent was removed to half under reduced pressure. The material was extracted with ethyl acetate, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was washed with hexane/ethyl acetate (8/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(1-ethyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.10g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.0 Hz), 1.34 - 1.45 (2H, m), 1.46 (3H, t, J = 7.4 Hz), 1.54 - 1.65 (2H, m), 2.62 (2H, m), 3.40 (2H, m), 3.56 (2H, t, J = 6.6 Hz), 3.78 - 3.84 (2H, m), 4.14 - 4.19 (2H, m), 4.29 (2H, q, J = 7.4 Hz), 4.86 (2H, s), 6.99 (3H, d, J = 8.8 Hz), 7.44 - 7.49 (3H, m), 7.58 (1H, d, J = 2.2 Hz), 7.88 (1H, s).

IR (KBr) 2957, 2932, 1667, 1609, 1505, 1435, 1273, 1244, 1119, 828, 797 cm<sup>-1</sup>.

Working Example 111 (Production of Compound 111)

In THF (6.0ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(1-ethyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.10g). To the solution was added DMF (two droplets), followed by addition of oxalyl chloride (35 $\mu$ l) at 0°C and stirring at room temperature for 1 hour. The solvent was removed under reduced pressure, a solution of the resulting residue in THF was added dropwise to a solution of 4-[methyl(tetrahydropyranyl-4-yl)aminomethyl]phenylalanine (50mg) and triethylamine (0.17ml) in THF (6.0ml) at 0°C, and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 3/1), which was recrystallized from hexane/ethyl acetate to give 7-[4-(2-butoxyethoxy)phenyl]-1-(1-ethyltetrazol-5-ylmethyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 111) (34mg).

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (3H, t,  $J = 7.2$  Hz), 1.33 - 1.45 (2H, m), 1.46 (3H, t,  $J = 7.2$  Hz), 1.57 - 1.75 (6H, m), 2.21 (3H, s), 2.68 (3H, m), 3.36 - 3.43 (4H, m), 3.51 -

3.59 (2H, m), 3.59 (2H, s), 3.77 - 3.83 (2H, m), 4.00 - 4.17 (4H, m), 4.32 (2H, q,  $J = 7.2$  Hz), 4.81 (2H, s), 6.98 (3H, d,  $J = 8.8$  Hz), 7.30 (2H, d,  $J = 8.4$  Hz), 7.42 - 7.82 (8H, m).

5 IR (KBr) 3277, 2934, 1651, 1607, 1505, 1242, 822  $\text{cm}^{-1}$ .

Reference Example 316

In THF (20.8ml)/methanol (20.8ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-(2-ethyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylate (1.04g).

10 To the solution was added 1N sodium hydroxide (10.4ml), and the mixture was stirred at 50°C for 4 hours. After cooled to room temperature, pH was adjusted to approximate 5 with 6N hydrochloric acid, and the solvent was removed to half under reduced pressure. The material  
15 was extracted with ethyl acetate, and the extract was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was washed with hexane/ethyl  
20 acetate (8/1) to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2-ethyltetrazol-4-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.76g).

$^1\text{H}$ -NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (3H, t,  $J = 7.0$  Hz), 1.33 - 1.45 (2H, m), 1.55 - 1.65 (2H, m), 1.66 (3H, t,  $J = 7.4$  Hz), 2.88 (2H, m), 3.45 (2H, m), 3.56 (2H, t,  $J = 6.6$  Hz), 3.81  
25 (2H, m), 4.13 - 4.18 (2H, m), 4.68 (2H, q,  $J = 7.4$  Hz),

4.77 (2H, s), 6.98 (2H, d,  $J = 8.8$  Hz), 7.17 (1H, d,  $J = 8.8$  Hz), 7.41 - 7.49 (3H, m), 7.55 (1H, d,  $J = 2.2$  Hz), 7.91 (1H, s).

IR (KBr) 3034, 2934, 1672, 1607, 1501, 1404, 1246, 1190,  
5 1132, 816  $\text{cm}^{-1}$ .

Working Example 112 (Production of Compound 112)

In THF (15ml) was dissolved 7-[4-(2-butoxyethoxy)phenyl]-1-(2-ethyltetrazol-5-ylmethyl)-2,3-dihydro-1-benzazepine-4-carboxylic acid (0.75mg). To the  
10 solution was added DMF (three droplets), followed by addition of oxalyl chloride (0.26ml) at  $0^{\circ}\text{C}$  and stirring at room temperature for 1 hour. The solvent was removed under reduced pressure. a solution of the resulting residue in THF was added dropwise to a solution of 4-  
15 [methyl(tetrahydropyranyl-4-yl)aminomethyl)phenylalanine (0.38g) and triethylamine (1.26ml) in THF (11.4ml) at  $0^{\circ}\text{C}$ , and the mixture was stirred at room temperature for 2 hours. The reaction solution was added to water. and the mixture was extracted with ethyl acetate. The extract  
20 was washed with saturated brine and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol=3/1), which was recrystallized from hexane/ethyl acetate to give 7-  
25 [4-(2-butoxyethoxy)phenyl]-1-(2-ethyltetrazol-5-

ylmethyl)-N-[4-[N-methyl-N-(tetrahydropyran-4-yl)aminomethyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 112) (0.48g).

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>) δ 0.93 (3H, t, J = 7.2 Hz), 1.33 - 1.45 (2H, m), 1.54 - 1.78 (6H, m), 1.66 (3H, t, J = 7.2 Hz), 2.21 (3H, s), 2.65 (1H, m), 2.95 (2H, m), 3.30 - 3.43 (2H, m), 3.46 - 3.50 (2H, m), 3.55 (2H, t, J = 6.6 Hz), 3.57 (2H, s), 3.77 - 3.83 (2H, m), 3.99 - 4.08 (2H, m), 4.12 - 4.18 (2H, m), 4.68 (2H, q, J = 7.2 Hz), 4.78 (2H, s), 6.98 (2H, d, J = 8.8 Hz), 7.18 (1H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.8 Hz), 7.39 - 7.59 (8H, m).

IR (KBr) 3306, 2934, 1644, 1505, 1244, 1140, 812 cm<sup>-1</sup>.

Anal. Calcd. C<sub>40</sub>H<sub>51</sub>N<sub>7</sub>O<sub>4</sub> Calcd. C, 69.24; N, 14.13; H, 7.41.

Found C, 69.04; N, 14.04; H, 7.44.

# 15 Working Example 113 (Production of Compound 27)

To a solution of 7-[4-(2-butoxyethoxy)phenyl]-1-propyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (4.00g) in THF (40ml) were added thionyl chloride (1.72ml) and DMF (0.5ml) at room temperature, and the mixture was stirred for 1 hour. After concentration under reduced pressure, the residue was dissolved in THF (50ml) and DMF (10 ml), which was added dropwise to a mixture of 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline dihydrochloride (3.05g) and

10018321.121201

triethylamine (7.9ml) in THF (30ml) at 0°C. After stirred at room temperature for 16 hours, water was added to the reaction system, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. After concentrated under reduced pressure, the residue was separated and purified with column chromatography (ethanol : ethyl acetate = 1 : 19), which was further purified by recrystallization (2-propanol) to give an end product (Compound 27) (4.19g) as yellow crystals.

#### Industrial Applicability

The compound of the formula (I) of the present invention or a salt thereof has potent CC chemokine receptor (CCR) antagonistic activity, in particular, potent CCR5 antagonistic activity and, thus, it can be advantageously used for the treatment or prevention of infectious disease of various HIV in human (e.g., AIDS).